CLINICAL REVIEW

Application Type	Supplemental NDA
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Priority or Standard	Standard
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Division / Office	Division of Neurology Products Office of New Drugs
Reviewer Name(s)	Emily R. Freilich, M.D.
Review Completion Date	September 29, 2017
Established Name	Lacosamide
(Proposed) Trade Name	Vimpat
Therapeutic Class	Anticonvulsant
Applicant	UCB, Inc.
Formulation(s)	Tablet, oral suspension
Dosing Regimen	2-12 mg/kg/day, max 400 mg daily
Indication(s)	Treatment of Partial Onset Seizures
Intended Population(s)	Patients 4 years old and above

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

VIMPAT is recommended for approval for the treatment of partial-onset seizures (POS) in patients who are 4 years of age and older, for use as both adjunctive therapy and monotherapy. There is adequate support for the safety and efficacy of VIMPAT tablets and oral solution for the treatment of partial-onset seizures in patients 4 to < 17 years of age. Additional safety information will be required to support the use of the intravenous formulation for POS in this age range. Efficacy and dosing recommendations are based on the extrapolation of efficacy from adult data with supportive clinical pharmacology pediatric pharmacokinetic (PK) data. The safety analysis did not reveal any new safety concerns.

1.2 Risk Benefit Assessment

The overall risk benefit analysis of VIMPAT in pediatric patients is acceptable. Pediatric patients with partial-onset seizures often suffer from debilitating epilepsy with high risk of status epilepticus, as well as associated learning and behavior difficulties and developmental delay. Despite the use of currently approved therapies, often as polypharmacy, many children continue to experience frequent seizures and require additional medication options.

The FDA has recently determined that extrapolation of efficacy from adults to pediatric patients age 4 years and older is appropriate for partial-onset seizures based on similar pathophysiology of POS in both adults and children in this age range, as well as a review of several marketed antiepileptic drugs showing similar exposure-response relationships in both pediatric and adult subjects with POS[1,2]. VIMPAT was approved for marketing in the US in 2008 for treatment of POS in adults. The clinical trials supporting that approval, along with PK modeling and simulation studies of the pediatric population, are used in this supplement to support evidence of effectiveness in children 4 years of age and older.

The safety profile of VIMPAT is well-characterized in adults. The submitted open-label, long-term safety data on 328 pediatric subjects between the ages of 4 years and 17 years did not reveal any new concerning safety signals, and common adverse events noted in pediatric subjects were similar to those noted in adults. No safety signal was identified.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

There are no new recommendations for additional postmarket requirements. Routine postmarket surveillance will continue.

2 Introduction and Regulatory Background

2.1 Product Information

Lacosamide (LCM) is a member of a series of functionalized amino acids that were synthesized specifically as candidates for anticonvulsant drug therapy. LCM has been shown to selectively enhance the slow inactivation of sodium channels, reducing neuronal hyperexcitability and thereby reducing seizure potential.

LCM is indicated for treatment of partial-onset seizures and was approved in October 2008 for adjunctive therapy, and in August 2014 for monotherapy for patients 17 years of age and older in both tablet (NDA 022253) and oral solution (NDA 022255, approved April 2010). It is also available in injection form (NDA 022254), for the indication of short-term management of seizures in adult patients with POS unable to tolerate oral therapy. The injection form is included by reference in this supplement for labeling purposes only, as all three forms share Full Prescribing Information, but is not recommended for use in pediatric patients pending the completion of further studies.

This supplemental application is to support extending the current indication for oral treatment of POS down to 4 years of age for use as either monotherapy or adjunctive therapy. Additional safety information will be required to support the use of the intravenous formulation for POS in this age range.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are many anticonvulsants approved for POS in adults, but only a smaller number are approved in children. The majority of approved products for pediatrics are for adjunctive therapy only.

Table 1. Currently available AEDS approved for POS

AED	Adjunctive therapy in Pediatric POS	Monotherapy in Pediatric POS
Levetiracetam	Yes (≥ 1 month)	No
Valproic Acid	Yes (age not specified in dosing but label mentions age 3 months)	Yes (≥ 10 years)
Topiramate	Yes (≥ 2 years)	Yes (≥ 2 years)
Lamotrigine	Yes (≥ 2 years)	No (yes ≥ 16 years)
Gabapentin	Yes (≥ 3 years)	No
Oxcarbazepine	Yes (≥ 4 years)	Yes (≥ 4 years)
Vigabatrin	Yes (10-16 years), but not first line due to safety issues	No
Tiagabine	Yes (≥ 12 years)	No
Perampanel	Yes (≥ 12 years)	No
Primidone	Yes, generally	No
Phenytoin	Yes (age not specified)	No
Carbamazepine	Yes (age not specified)	No
Phenobarbital	seizure type not specified in label	No
Eslicarbazapine	Yes (≥ 4 years)	Yes(≥ 4 years)
Zonisamide	No	No
Pregabalin	No	No
Ezogabine	No	No
Felbamate	No*	No
Rufinamide	No*	No
Clobazam	No*	No

*Approved for pediatric patients with Lennox-Gastaut Syndrome (LGS)

2.3 Availability of Proposed Active Ingredient in the United States

Lacosamide is approved and currently marketed as VIMPAT in the United States for treatment of POS in patients 17 years and older as noted in Section 2.1, and is thus readily available in both tablet and oral solution.

2.4 Important Safety Issues With Consideration to Related Drugs

The following warnings and precautions are currently in the VIMPAT label and are thus safety considerations for this supplement:

- Cardiac rhythm and conduction abnormalities,
- Suicide behavior and ideation,
- Syncope,
- Dizziness and Ataxia,
- Gradual withdrawal of drug, and

- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/ Multi-organ Hypersensitivity Reactions.

Additionally, the analysis includes the potential risks for hepatotoxicity, serious skin reactions, and falls/injuries associated with many anticonvulsant medications, although not specifically included in the Warnings and Precautions section of the VIMPAT label.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

As noted above, VIMPAT was originally approved for adjunctive treatment of partial-onset seizures in adults 17 years and older on October 28, 2008 in both tablet form and injection. The oral suspension was approved on April 20, 2010 for the same indication, and all forms were approved for use as monotherapy in the same population on August 29, 2014.

The basis for this pediatric supplement is the extrapolation of efficacy from adults to children, as well as the extrapolation of safety and efficacy from adjunctive therapy to monotherapy, and is supported by General Advice letters sent from FDA to the sponsors of epilepsy-related products in November 2015 and September 2016, respectively.

In our General Advice letter dated November 12, 2015, we outlined the basis for our acceptance of pediatric extrapolation in the treatment of partial-onset seizures and the requirements necessary to support such an indication. We determined that POS in pediatric patients 4 years of age and older are similar to POS in adults, and analysis of multiple antiepileptic drugs demonstrated a similar exposure-response relationship in both pediatric and adult patients with POS.[1]

The requirements to support an indication for treatment of POS in pediatric patients age 4 and older that relies upon extrapolation include:

- An approved indication for the treatment of POS in adults.
- A pharmacokinetic analysis to determine the dosing regimen that provides drug exposures in pediatric patients age 4 and older similar to those in adult patients at levels demonstrated to be effective in adults.
- Long-term, open-label, safety studies in pediatric patients 4 years of age and older.

Furthermore, a second General Advice letter was sent on September 13, 2016 stating that extrapolation can be used by similar principles to extrapolate effectiveness of

monotherapy if there is an approved indication for adjunctive therapy with the appropriate pharmacokinetic analyses.

After receipt of the General Advice letter, the applicant requested a Type B pre-sNDA meeting to discuss this pediatric extrapolation submission, which was a teleconference held on September 8, 2016. At that time, the applicant indicated their plans to submit pediatric PK and safety data to extend the indication for the treatment of partial onset seizures down to pediatric patients age 4 years and over, for both adjunctive and monotherapy use. (b) (4) During that meeting, the Agency outlined that the applicant should provide available safety data from pediatric exposures in all age ranges, including < 4 years of age; however, the extrapolation would only apply to pediatric patients age 4 years and older. We also emphasized that the safety analysis should also address adverse events of interest for the epilepsy population, such as DRESS, injuries and falls, which the applicant proposed to submit as part of their 120-day safety update.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the electronic submission was acceptable. The NDA supplement was submitted in eCTD format and conformed to CDISC SDTM standards. The information required for the review of the NDA was well organized, easy to navigate, and complete.

3.2 Compliance with Good Clinical Practices

The applicant states that the studies were conducted in accordance with good clinical practice, including archiving of essential documents.

3.3 Financial Disclosures

The applicant provided required information regarding financial disclosures and there was no evidence that significant bias was introduced into the results of these trials.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

VIMPAT is an already approved product. CMC information was submitted regarding compatibility of the VIMPAT oral solution with feeding tube use and the studies were found to be acceptable by CMC.

4.2 Clinical Microbiology

No Clinical microbiology studies were included in this NDA supplement.

4.3 Preclinical Pharmacology/Toxicology

A nonclinical program to support the pediatric clinical development was previously conducted and the results of a chronic toxicity study in juvenile beagle dogs completed in 2009 was submitted for review with this supplement.

Please see the complete Pharmacology/Toxicology Review for a review of this study.

4.4 Clinical Pharmacology

Efficacy in pediatric patients with partial-onset seizures ≥ 4 years of age is based on extrapolation of dose-exposures in the adult population to that of the pediatric population.

4.4.1 Mechanism of Action

The precise mechanism by which VIMPAT exerts its antiepileptic effects in humans remains to be fully elucidated. *In vitro* electrophysiological studies have shown that LCM selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing.[3]

4.4.2 Pharmacodynamics

No specific studies evaluated the LCM pharmacodynamic effects in pediatric subjects. The ECG results in pediatric subjects were consistent with those observed in adult studies (see Section 7.4.4), therefore, the following pharmacodynamic correlations between LCM concentration and ECG parameters noted in adults are expected to be similar in pediatric subjects down to 4 years of age.

In studies of adult subjects with epilepsy, increasing plasma concentration of LCM were associated with a small prolongation of the PR interval, but not with a prolongation of the QT interval. Weak correlations between increasing plasma LCM concentrations and slight prolongations of the QRS interval were observed in two adult studies (SP667, SP754); however, a similar correlation was not observed in a third study of adult subjects (SP755).

There were no clinically significant effects of VIMPAT on vital signs in the studies submitted in this application.

4.4.3 Pharmacokinetics

The pharmacokinetics of VIMPAT have been studied in healthy adult subjects (age range 18 to 87 years), adults with partial-onset seizures, adults with diabetic neuropathy [not an approved indication], and subjects with renal and hepatic impairment.

The applicant performed a pooled population PK analysis based on data collected from pediatric patients with partial-onset seizures in Studies SP1047 and SP847. Using the pediatric population PK model, the applicant conducted PK simulations to arrive at pediatric dose selections, which are likely to match exposures in adults receiving approved LCM doses. Using pediatric data from the population PK analysis, the applicant conducted PK simulations in virtual adult patients and virtual pediatric patients in order to derive pediatric dosing for both initial dosing and maintenance dosing.

The applicant proposed weight-based dosing adaptations of LCM to approximate the steady-state LCM plasma concentrations observed in adults with POS taking the maximum therapeutic dose of 400 mg/day. See final approved label for complete dosing recommendations.

Please see the Office of Clinical Pharmacology review for a full discussion of methods and issues related to pharmacokinetics in the pediatric studies.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2. Studies of Pediatric Subjects with Partial Onset Seizures

Study ID	Study Design	Study population	# subjects	Dosing and Duration	Study Status
SP0847	Phase 2, multicenter, open-label, dose-titration study	Pediatric subjects age 1 month to 17 years with uncontrolled partial-onset seizures	N = 47	2-12 mg/kg/day (8 mg/kg/day in Cohort 1) Up to 6 weeks	Completed
SP0848	Phase 2, multicenter, long-term, open-label extension study	Pediatric subjects age 1 month to 17 years with epilepsy (previously enrolled in SP0847, SP0966*, or directly enrolled)	N = 177	2-12 mg/kg/day dose titration Up to 2 years	Ongoing
SP1047	Phase 1, open label, multicenter PK study	Pediatric subjects age 1 month to 17 years with epilepsy on commercial LCM	N = 32	Dose prescribed by outpatient doctor for last 7 days Single dose	Completed
EP0034	Phase 3, multicenter, open-label long term extension study of safety and efficacy	Pediatric subjects age 1 month to 17 years with partial onset seizures (previously enrolled in SP0967* and SP0969*)**	N = 159	2-12 mg/kg/day Up to 2 years	Ongoing

* Data from subjects enrolled in SP0966, SP0967, and SP0969 are not submitted in this supplement because the studies were still blinded at the time of the submission.
**EP0034 safety data included only patients who enrolled from SP0969, as they are all between ages 4 years and 17 years with POS

5.2 Review Strategy

This clinical review is focused on safety in pediatric patients with partial-onset seizures. Safety data was submitted on all pediatric subjects with POS enrolled in the studies SP847, SP848, and EP0034 who received at least one dose of oral LCM. Safety data from SP1047 was not included in the analysis as it was a single dose study and safety information was limited, although it did not reveal any serious safety concerns.

All the data was reviewed independently and I conducted my own analyses of the submitted safety data. All the lab results and the submitted narratives from each study were individually reviewed to identify new safety concerns that differed from the current prescribing information.

The data submission also included data on 15 subjects under the age of 4 who were enrolled in SP847. These data were not included in my analyses but were reviewed for any concerning safety signals and for Serious Adverse Events (SAEs).

Data from subjects age 16 years and older were included in my analyses, as the current approval is only down to age 17 years.

The 120-day safety update was submitted in May 2017 and was reviewed for any serious safety concerns that occurred after the clinical cutoff date for the initial submission. The LCM drug safety moiety update from all completed and ongoing studies in adults and pediatric subjects, including analysis for any incidents of DRESS, falls, and injuries, was also reviewed for any safety concerns. Finally, all available postmarketing data, including all data collected from off-label use of commercial VIMPAT in the pediatric population were reviewed as well.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study SP847

Study SP847 is 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.

Subjects in this study had a maximum treatment duration of 6 weeks with the option to enroll in the long-term open-label study (SP848). Doses were titrated up to 8-12 mg/kg/day (not to exceed 600 mg/day) in increments of 2 mg/kg/day at weekly intervals. Subjects discontinued when they achieved maximum tolerated dose (dose reduction for any reason) and had blood samples collected for PK analysis.

Forty-seven subjects started the study (including 15 subjects age 1 month to 4 years), and 24 subjects completed the study. Twenty-three subjects discontinued the study due to predefined requirements of the study; however, all but seven subjects subsequently enrolled in the long-term extension study.

5.3.2 Study SP848

SP848 is 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.

Subjects were previously enrolled in either SP847, SP0966 (pediatric patients with primary generalized seizures), or directly enrolled into the study. SP848 was also designed to obtain preliminary efficacy data on seizure frequency, and included a cohort of 46 Japanese subjects aged 4-17 years. Subjects who enter from a prior study (SP847 or SP0966) began on the LCM dose they were receiving at end of

the previous pediatric study. If they enrolled directly into SP848, they started at 2 mg/kg/day and titrated in increments of 2 mg/kg/day weekly to optimal level not to exceed 12 mg/kg/day or 600 mg/day.

Subjects were able to receive LCM for up to 2 years, although subjects in Japan will continue until the date of market approval or discontinuation of development of LCM. Interim safety results as of the clinical cutoff date of May 2, 2016 were submitted, excluding subjects from SP0966 as they had a diagnosis of primary generalized seizures. At the time of the cutoff date, 177 subjects had started the study.

5.3.3 Study EP0034

Study EP0034 is 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.

Subjects were previously enrolled in SP0967 or SP0969 (double blind placebo-controlled studies) in North America, Europe, Latin America, and the Asia/Pacific regions. There was a transition period at end of the primary study and then subjects were transitioned to a dose of LCM according to their weight, either 10 mg/kg/day (< 30 kg), 6 mg/kg/day (30-50 kg), or 300 mg/day (≥ 50 kg) during their first week in the treatment period. Then doses were adjusted based on clinical judgment.

Interim safety results as of the clinical cutoff date of May 2, 2016 were submitted, excluding subjects who enrolled into EP0034 from SP0967, who are all < 4 years of age and outside the target age group for this submission. At the time of clinical cutoff date, 159 subjects had started the study.

5.3.4 Study SP1047

SP1047 is a Phase 1, single dose pharmacokinetic study of commercially available LCM in pediatric subjects prescribed LCM by their regular physicians after being on a stable dose for 1 week. As it was a single dose study, safety data was limited on these subjects. There were no new serious safety concerns in this single dose study, and data is not further reviewed or included in the analyses below.

6 Review of Efficacy

Efficacy Summary

No clinical studies were submitted for efficacy review in this supplement. Evidence for the effectiveness of VIMPAT in POS patients age 4 years to < 17 years is based on the prior finding of efficacy in adults with POS, and also on PK modeling and simulation to develop dosing recommendations that provide similar exposures to those that were found to be therapeutic in adult patients. Evidence for the effectiveness of monotherapy use of VIMPAT in POS 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 and adjunctive use of VIMPAT. See Section 2.5 for further information on extrapolation.

Of note, the Applicant did submit a final study report for Study SP0969, a double-blind, randomized, placebo-controlled study of VIMPAT in pediatric subjects with partial-onset seizures between ages 4 to < 17 years late in the review cycle of this sNDA. The final study report was submitted to the associated IND (057939/073809) and the efficacy results were as follows:

- (b) (4)
-

The datasets from the study were not submitted or reviewed as part of this sNDA, so the findings of the study report have not been independently confirmed.

7 Review of Safety

Safety Summary

VIMPAT is already approved for treatment of partial onset seizures in patients age 17 years and older for use as adjunctive therapy (2008) and monotherapy (2014). This VIMPAT sNDA submission includes safety data on 328 pediatric subjects over age 4 years, pooled from three individual open-label studies (SP0847, SP0848, and EP0034) into safety pool SPX-1.

The safety population included all subjects in these studies who were between the ages of 4 years and 17 years, had partial-onset seizures, and received at least one dose of LCM. The clinical safety monitoring conducted in these trials was appropriate and adequate to identify major safety signals. The safety findings overall are consistent with data from the original NDA submission for treatment of partial-onset seizures in adults. No new safety signals were identified. The safety profile was consistent with that of the adult epilepsy safety profile as described in the current VIMPAT prescribing information.

Table 3 summarizes the relative incidence of different types of treatment emergent adverse events (TEAEs) noted in the safety population. There was one death during the study that is reviewed in detail below in Section 7.3.1. Serious adverse events, adverse events of severe intensity, significant adverse events of interest, and common adverse events are analyzed and described in the following sections.

Table 3. Number of subjects experiencing each type of Adverse Event

	≥ 4 to < 12 years N = 189 n (%)	**≥ 12 to < 16 years N = 105 n (%)**	**≥ 16 years N = 34 n (%)**	**Total (all ages) N = 328 n (%)**
Total TEAEs	158 (83.6)	81 (77.1)	31 (91.1)	270 (82.3)
SAEs	34 (18.0)	10 (9.5)	8 (23.5)	52 (15.9)
TEAEs leading to D/C	13 (6.9)	5 (4.8)	1 (2.9)	19 (5.8)
TEAEs - Severe	14 (7.4)	7 (6.7)	2 (5.9)	23 (7.0)
Deaths	0	1 (0.1)	0	1 (0.3)

Source: Clinical reviewer's analysis of the Pool SPX-1 data of Subjects over age 4

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The applicant submitted data from three studies to support the safety of VIMPAT in pediatric patients. Study details are outlined above in Section 5.1. The safety data from subjects with partial-onset seizures enrolled in SP847, SP848 and EP0034 who received at least one dose of LCM were submitted and pooled together into data Pool SPX-1 for a combined 343 pediatric subjects. Fifteen of these subjects were under 4 years of age, and were excluded from the remainder of the analysis, leaving 328 pediatric subjects included in this review.

Data submitted on the 15 subjects under 4 years of age were reviewed for any serious safety concerns but were not included in any of the major analyses. No new safety signals were identified in this population. There was one case of drug-induced liver injury in a one-year-old that is described in more detail under serious adverse events (Section 7.3.2).

Study SP1047 was not included in the analysis for the safety review, as it was a single-dose study with minimal safety information provided, although the PK data contributed to the PK modeling and simulation studies reviewed by the clinical pharmacology team to support dosing recommendations.

Postmarketing safety data from pediatric off-label use of commercially available LCM was also reviewed from 1077 cases totaling over (b) (4) patient-years of exposure across the age group of 4 to <17 years of age. The postmarketing data is summarized below in Section 8, and was reviewed for any significant safety signals.

The applicant also submitted a 120-day Safety Update during the review cycle. This safety update included data on adverse events occurring beyond the clinical cutoff date, as well as an analysis on the incidence of DRESS and falls/injuries from all studies involving LCM, which the division requested at our pre-sNDA meeting. The safety update was reviewed for major safety signals (see Section 7.7).

As noted above, 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 during the review cycle of this sNDA. The final study report was submitted to INDs 057939/073809. The datasets from the study were not submitted for review as part of this sNDA, but a high-level review of the efficacy and safety results described in the study report was completed and is summarized below (Section 7.7).

7.1.2 Categorization of Adverse Events

The applicant defined adverse events (AEs) as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. AEs were coded by MedDRA System Organ Class (SOC) and Preferred Term (PT) using MedDra dictionary version 16.1.

Treatment-emergent adverse events (TEAEs) were defined as “those AEs starting after first dose of study drug through 30 days following the last dose of LCM (or up to clinical cutoff date of May 2, 2016)”.

Serious Adverse Events (SAEs) are defined as a TEAE that meets one or more of the following criteria:

- Death,
- Life-threatening,
- Significant or persistent disability/incapacity,
- Congenital anomaly/birth defect (including that occurring in a fetus),

- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition of serious,
- Initial inpatient hospitalization or prolongation of hospitalization.

Data was pooled from three open-label studies SP0847, SP0848, and EP0034. There was no controlled safety data with age-matched placebo controls for any of the studies.

The safety analysis focused on treatment-emergent adverse events (TEAEs), SAEs, severe TEAEs, most common TEAEs, and those TEAEs that led to discontinuation. The applicant also identified significant adverse events of interest using the known safety profile of both VIMPAT as well as other antiepileptic drugs (AEDs).

These significant AEs of interest included hepatotoxicity-related terms, cardiac- and ECG-related terms, suicidality-related terms, syncope, and loss of consciousness. At the division's request, incidence of DRESS (Multi-organ Hypersensitivity), injuries, and falls were also analyzed. Other seizure-related adverse events of interest were memory impairment, amnesia, cognitive disorder, and psychotic symptoms.

Finally, given the pediatric study population, TEAEs related to pediatric growth, neurodevelopment, behavior and endocrine were also analyzed separately for incidence, severity, relationship to LCM, seriousness, and contribution to discontinuation.

Some AE codes were coded under slightly different terms despite being similar processes. Therefore, several terms were recoded to avoid underestimating prevalence of a specific adverse event, or class of adverse event. Some terms were also recoded for ease of review, although none rose to the level of a new safety concern. The following table shows the original AE code on the left, and revised codes on the right. Terms that only resulted in the addition of one or two cases after recoding are not included in the table.

Table 4: Recoded AE Codes to Group Similar Terms

Original Coded Term	**Recoded Term**
Abdominal pain upper, Abdominal discomfort	Abdominal pain
Complex Partial Seizures, Convulsion, Partial Seizures, Partial Seizures with Secondary Generalization, Seizure Cluster	Seizures
Anxiety Disorder	Anxiety
Allergic Rhinitis	Rhinitis
Vision blurred	Visual impairment
Cerebellar Ataxia	Ataxia

Allergic Conjunctivitis, Bacterial Conjunctivitis	Conjunctivitis
Viral Gastroenteritis	Gastroenteritis
Viral Pharyngitis, Streptococcal Pharyngitis	Pharyngitis
Ear infection, Acute Otitis Media	Otitis Media
Aspiration Pneumonia, Bacterial Pneumonia	Pneumonia
Viral Respiratory Tract Infection	Respiratory Tract Infection
Viral Upper Respiratory Tract Infection	Upper Respiratory Tract Infection
Rash papular, Rash scarlatiniform, Rash erythematous	Rash

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

As mentioned above, all subjects with partial-onset seizures from studies SP847, SP848, and EP0034 who received at least one dose of LCM were pooled together into Safety Population Pool SPX-1 for review and then analyzed with removal of subjects under 4 years of age (328 subjects).

All data for this submission is open-label, so there is no control population, and pooling of subjects from all trials was acceptable.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The exposure duration and doses were appropriate for adequate safety review. There were a total of 328 subjects between ages 4 years and 17 years that received at least one dose of LCM. There were equal proportions of male and female subjects, with a predominance of white subjects, mainly from North America and Eastern Europe. See Table 5 (Demographics) and Table 6 (Exposure data) below.

Table 5. Demographics of the Safety Population

	TOTAL N = 343 (%)
AGE	
< 4 years	15 (4.4)
4 to < 12 years	189 (55.1)
12 to < 16 years	105 (30.6)
≥ 16 years	34 (9.9)
GENDER	
Male	178 (51.9)
Female	165 (48.1)
RACE	
White	227 (66.2)
Black	22 (6.4)
Asian	78 (22.7)
Other/Mixed	16 (4.7)
ETHNICITY	
Hispanic or Latino	42 (12.2)
Not Hispanic or Latino	301 (87.80)
COUNTRY/REGION	
Asia/Pacific/Other	80 (23.3)
Eastern Europe	133 (38.8)
Latin America	14 (4.1)
North America	96 (28.0)
Western Europe	20 (5.8)

Source: Clinical reviewer's analysis of the Pool SPX-1 data.

Table 6: Duration of Exposure by Age

	≥ 4 to < 12 years N = 189	**≥ 12 to < 16 years N = 105**	**≥ 16 years N = 34**	**Total (all ages) N = 328**
Duration				
> 0 months	189	105	34	**328**
> 6 months	139	77	30	**246**
> 12 months	85	50	13	**148**
> 18 months	57	31	7	**95**
> 24 months	37	18	4	**59**

Source: Clinical reviewer's analysis of the Pool SPX-1 data of Subjects over age 4

The modal daily dose, or the dose the subject spent the most time on, not the maximum dose, is illustrated in the table below, categorized by weight band (Table 7). Overall, patients under 30 kg tended to both require and tolerate higher doses. The following table (Table 8) also illustrates the duration of exposures by modal daily dose.

Table 7: Modal Daily Dose Range by Weight

Modal Dose	≤ 30 kg N =123	30-50 kg N =107	≥ 50 kg N= 98	Total N = 328 (%)
0-4 mg/kg/day	8	4	14	26 (7.9)
4-6 mg/kg/day	8	9	45	62 (18.9)
6-8 mg/kg/day	22	38	21	81 (24.7)
8-10 mg/kg/day	22	27	15	64 (19.5)
10-12 mg/kg/day	40	22	3	65 (19.8)
≥ 12 mg/kg/day	23	7	0	30 (9.1)

Source: Clinical reviewer's analysis of the Pool SPX-1 data of Subjects over age 4

Table 8: Duration of Exposure by Modal Daily Dose

	0-4 mg/kg/day N = 26	4-6 mg/kg/day N = 62	6-8 mg/kg/day N = 81	8-10 mg/kg/day N = 64	10-12 mg/kg/day N = 65	≥ 12 mg/kg/day N = 30	Total N = 328
Duration							
> 0 months	26	62	81	64	65	30	328
> 6 months	13	47	57	53	50	26	246
> 12 months	7	25	37	29	34	16	148
> 18 months	3	14	22	24	22	10	95
> 24 months	2	5	12	16	15	9	59

Reviewer's comments: This efficacy supplement for an already approved product is to extend the indication into a vulnerable population, pediatric patients down to age 4 years. I feel that the size and exposure duration of the safety population is adequate and appropriate given the vast experience with the drug in adult populations.

The patient demographics are representative of the target age population with no sex discrepancies. The studies are in predominantly white subjects; however, a modest number of subjects of other races and ethnicities are included to evaluate safety and appears adequate.

A wide range of doses was explored and doses were titrated individually for each patient for efficacy and tolerability. The overall dose range was adequate with acceptable number of subjects at each dose.

7.2.2 Explorations for Dose Response

Throughout all of the open-label studies, the doses were titrated by weight from 2 mg/kg/day up to 12 mg/kg/day (and occasionally higher) and titrated for tolerance and effectiveness. There was no placebo-controlled or blinded data to review for dose response curves.

7.2.3 Routine Clinical Testing

Routine clinical testing included physical and neurological examinations, vital signs (blood pressure and pulse), body weight and height, 12-lead ECGs, laboratory testing (hematology, chemistry, including hepatic function (AST, ALT, Alk Phos, total bilirubin and GGT), endocrine function, and urinalysis), and assessment of adverse events. The assessments and frequency of assessments completed during the studies were reasonable and appropriate.

7.2.4 Metabolic, Clearance, and Interaction Workup

Please refer to the Office of Clinical Pharmacology Review.

7.2.5 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

VIMPAT is already approved in the United States for treatment of partial-onset seizures in patients 17 years of age and older; hence, the adverse event profile is relatively well characterized. The significant AEs of interest outlined above are representative of the known adverse reactions of VIMPAT as well as the known adverse reactions of other antiepileptic drugs in populations of patients with partial onset seizures.

7.3 Major Safety Results

7.3.1 Deaths

There was one pediatric death in the safety population. The details of the subject's death are outlined below.

- Subject SP0969-224-19840 was a 13-year-old Asian male with multiple medical problems including a history of autism spectrum disorder, emotional disorder, migraine, encephalitis, and mental impairment, as well as partial seizures. Concomitant medications included clobazam, oxcarbazepine, levetiracetam, methylphenidate, flunarizine and pyridoxine. He enrolled in study EP0034 on September 24, 2015 after completion of double-blinded study SP0969 and died on (b) (6). He was receiving 150 mg twice daily LCM at the time of his death. He was found apneic and asystolic on the floor of his garage, and could not be resuscitated. Autopsy was denied, but a sternotomy for cardiac massage revealed blunt trauma, as well as a longitudinal sternal fracture with lacerations to his inferior vena cava and pulmonary artery. The death was reported as possibly related to suicide or suspected car accident. He did have a history of two reported prior suicide attempts, although this is disputed by patient's mother.

There were no known adverse events during the study and he had negative suicide screenings during study.

Reviewer's note: The exact cause of death is unknown in this subject given the available details; however, causality from LCM is unlikely given the reported blunt trauma and possible car accident. There are multiple confounding medical problems and concomitant medications to assign causality even in the case of possible suicide. A review of suicide-related terms is outlined below in Section 7.3.5 with no serious safety signal for suicidal behaviors for VIMPAT in pediatric subjects. Suicidality is listed in the Warnings and Precautions section of the current label.

There were two additional pediatric deaths reported in the120-day safety update submitted in May 2017 that occurred after the clinical cutoff date in different patient populations. These are briefly summarized here.

- Subject 364-19865 was a 10-year-old white male who died from status epilepticus and infection. He had a history of intraventricular hemorrhage, hydrocephalus, ventricular drain, mental retardation, sleep disorder and muscle hypotonia and was on several concomitant medications. He entered study EP0034 on (b) (6) and was receiving 9.1 mg/kg/day for an extended period. He died on (b) (6), after 388 days on LCM. On the morning of his hospitalization, he awoke with high fever, seizures, and arrived cyanotic and in status epilepticus at the hospital. He was intubated but despite aggressive treatment became asystolic, and resuscitation was unsuccessful.

- Subject 104-09103 from Study SP848 (started from study SP0966, history of generalized seizures) was a 16-year-old female with complex past medical history who died from presumptive sudden unexpected death in epilepsy patients (SUDEP). She had a history of lissencephaly, cerebral palsy, gastroesophageal reflux disease, and tracheostomy, and suffered from generalized seizures. She had been on LCM since May 3, 2016. She died on (b) (6), while taking LCM 75 mg twice daily. She was found unresponsive by her mom, shortly after a tube feeding, with no signs of respiratory distress and cause of death was never determined.

Review of the postmarketing data also revealed 14 deaths in the pediatric population between the ages of 4 years and 17 years. Three of these deaths were related to SUDEP, and the other 11 had alternative etiologies with underlying disease states that led to death. There was no evidence of causality of LCM in any of the postmarketing deaths.

Reviewer's note: The follow-up deaths from the safety update and postmarketing data do not appear related to the medication and do not raise a significant safety concern.

7.3.2 Nonfatal Serious Adverse Events

There were 52 pediatric subjects over age 4 years, who experienced a total of 129 serious adverse events (SAEs). The most common SAEs were seizures (24 subjects) and status epilepticus (7 subjects) leading to hospitalization, events which are common in this pediatric epilepsy patient population. Of the other SAEs, the majority appeared unrelated to the drug treatment, such as pneumonia, respiratory distress, and influenza (See Table 8), or are already labeled adverse events. For a further discussion of vomiting, (6 subjects), see Section 7.4.1 Common Adverse Events.

Table 9: Serious Adverse Events (SAEs) by System Organ Class

SAE by System Organ Class	No. Subjects
Nervous System Disorders	
Seizures*	24
Status epilepticus	7
Headache	2
Somnolence	2
Gastrointestinal disorders	
Vomiting	6
Constipation	3
Diarrhea	3
Abdominal Pain	2
Hematemesis	2
Metabolism and nutrition disorders	
Dehydration	3
Decreased appetite	2
Psychiatric disorders	
Mental status changes	3
Infections and infestations	
Gastroenteritis	2
Otitis media*	3
Pneumonia*	3
Urinary Tract Infection*	2
Upper Respiratory Tract Infection*	2

*Includes similar coded terms (recoded as per Table 3)
Source: Clinical reviewer's analysis of the Pool SPX-1 data of Subjects over age 4

The following SAEs were recorded in one subject each: Dizziness, hemorrhage intracranial, lethargy, neurotoxicity, paresthesia, psychomotor skills impaired, cranial nerve VII paralysis, coagulopathy, diplopia, gastrointestinal inflammation, Mallory-Weiss syndrome, nausea, pancreatitis, adverse drug reaction, chest pain, death, hypothermia, pyrexia, adenovirus infection, dengue fever, influenza, rhinovirus infection, clavicle fracture, head injury, weight decreased, malnutrition, agitation, emotional disorder of childhood, hallucination (auditory), nightmare, sleep disorder, suicide attempt, hematuria, nephrolithiasis, hypoventilation, hypoxia, respiratory distress, respiratory failure, sleep apnea syndrome, rash.

Three subjects had SAEs that led to discontinuation but none of the three appeared related to the drug. One of these three subjects was the above-mentioned death. Another subject suffered an intracranial hemorrhage following intracranial grid placement for surgical resection of seizure focus. The final subject suffered an episode

of aspiration pneumonia with associated hypoxia, lethargy and hypothermia that ultimately led to discontinuation from the study.

Reviewer's comment: The narratives from all the SAEs were reviewed. Many of the events were confounded, lacked sufficient information for evaluation, or there were not a sufficient number of events to suggest a new signal. The remainder of the events are already included in the VIMPAT label, and were consistent with those seen in the adult studies. No new signals unique to the pediatric population were identified.

7.3.3 Dropouts and/or Discontinuations

Reasons for study discontinuation are outlined in the table below. Nineteen subjects discontinued from the studies secondary to TEAEs. Three of these were mentioned above in Section 7.3.2 as they were also SAEs leading to discontinuation (death, intracranial hemorrhage and aspiration pneumonia).

Table 10: Treatment Status and Reason for Discontinuation

	Total N = 328 n (%)
Completed	49 (15.0)
Ongoing	200 (61.0)
Discontinued	79 (24.1)
Reasons for D/C:	
Adverse Event	19 (5.8)
Consent w/d	16 (4.9)
Lack of Efficacy	34 (10.4)
Lost to follow up	3 (1.0)
Other	8 (2.4)

Other = surgery, relocation, breakthrough seizures, parental request and no longer met inclusion criteria
Source: Clinical reviewer's analysis of the Pool SPX-1 data of Subjects over age 4

The remainder of the TEAEs leading to discontinuation were not serious. The most frequent reported TEAEs leading to discontinuation were dizziness (5), convulsion (4), aggression (2), and vomiting (2). Convulsions are expected in this patient population. Dizziness, aggression, and vomiting are already included in the label.

The remainder of the discontinuations related to TEAEs were individuals who discontinued due to single reports of "abnormal behavior", "blindness", and "QT prolongation", which are briefly reviewed below.

- The TEAE of blindness was reported in a 15-year-old female with a history of hepatitis A, HSV (herpes simplex virus) meningoencephalitis, and

attention-deficit-hyperactivity disorder (ADHD) who developed a verbatim term of “loss of vision” associated with moderate intensity nausea, vomiting, dizziness, and abdominal pain upper. She had just increased her dose of LCM to 10 mg/kg/day when symptoms began and she discontinued from the study as a result; however, her symptoms resolved within one day with no neurologic sequelae.

Reviewer’s comment: Due to the vague complaint, associated symptoms and rapid resolution, I do not feel this represents a new safety signal.

- A 15-year-old female subject reported abnormal behavior leading to discontinuation, with the verbatim term of “behavior problems”. She was on 10 mg/kg/day of LCM, and had been for 410 days, when the TEAE occurred. The event was reported as moderate and nonserious, and the symptoms did recover after withdrawal of the study drug.

  Reviewer’s comment: The complaint is again vague, and 410 days is a long latency for event to assign causality. Further discussion of abnormal behavior as an AE can be found in Section 7.4.1.

- A 6-year-old female experienced QT prolongation on 10 mg/kg/day of LCM with her QT increasing from 305.5 to 366.5 milliseconds. She did have a history of ventricular arrhythmia in the past. Her symptoms resolved with discontinuation of the drug.

  Reviewer’s comment: QT prolongation is already labeled for VIMPAT.

Of note, there were also two discontinuations due to TEAEs in the population under 4 years of age. One subject discontinued for “rash” which was described in a 3-year-old who had been on LCM for 17 days, and was also on lamotrigine. It was moderate in intensity, not serious, but did lead to discontinuation. The subject had been on 6 mg/kg/day for two days when the rash appeared. The rash resolved upon discontinuation. This case is confounded by use of lamotrigine; however, rash is already included in the label for adverse events.

There was also one a one-year-old subject with a history of Tuberous Sclerosis who reported drug-induced liver injury (DILI). The subject was noted to meet criteria for DILI on Day 20, four days after titrating to 6 mg/kg/day. The highest liver function tests reported were AST 215, ALT 401, ALP 557, GGT 346 and Bilirubin 3.4. She did not meet criteria for Hy’s law. Her concomitant medications were valproate, phenytoin, and topiramate. The LCM was discontinued and symptoms resolved within a few days. This case is confounded by multiple concomitant medications known for possible liver toxicity, and elevated liver enzymes are already included in the label for adverse events.

Reviewer's comment: Review of the TEAEs leading to discontinuation did not introduce any new safety signals. All the events were either already in the label, confounded, lacked sufficient information for evaluation, or there were not a sufficient number of events to suggest a new signal.

7.3.4 Significant Adverse Events

Significant adverse events included all TEAEs of severe intensity. Twenty-three subjects had a TEAE that was graded to be of severe intensity, only two of which led to discontinuation and were also SAEs already discussed above (death and intracranial hemorrhage, see Section 7.3.2).

The following severe TEAEs occurred in more than one subject: status epilepticus (6), convulsion (5), pneumonia (2), and vomiting (2). As mentioned above, these events are not concerning for new safety signals, as status epilepticus and convulsion are expected to occur in this patient population, and pneumonia and vomiting are already labeled AEs.

7.3.5 Submission Specific Primary Safety Concerns

As mentioned above, the applicant outlined a number of other non-fatal safety concerns as significant due to known risks within both the epilepsy population and the pediatric population, as well as the known safety profile of VIMPAT. These events were classified as "predefined significant TEAEs" as well as adverse events unique to the seizure population, and the results are summarized below. There were no new safety signals identified in the analysis of these specific TEAEs of interest.

- Cardiac Events
  Two subjects had a nonserious event of QT prolongation. One subject had a nonserious event of bundle branch block, which was mild and did not lead to discontinuation of drug. Another subject was a 17-year-old who was noted to have bradycardia, with a heart rate of 55-57 beats per minute, but this was not considered markedly abnormal and did not lead to discontinuation (*see also* Section 7.3.3 and Section 7.4.4).

- Loss of Consciousness
  No subjects met the predefined TEAE criteria for loss of consciousness.

- Syncope
  One subject had a mild episode of syncope that did not lead to discontinuation.

- Suicidal Ideation

Suicidal ideation (SI) was reported in three subjects (ages 10, 15, and 16 years) but all the events were considered nonserious and did not lead to discontinuation. There was a single report of self-injurious behavior in a 5-year-old which was nonserious and did not lead to discontinuation.

There was one SAE of suicide attempt in a 10-year-old (who also had SI listed above). It did not result in discontinuation from the study; however, after the study cutoff date, the same subject had another suicide attempt resulting in discontinuation from study.

- Hepatotoxicity
  No subject met the criteria for pre-defined hepatotoxicity, except for the one-year-old with presumed DILI described above in serious adverse events (Section 7.3.2).

- Falls and Injuries
  There were two serious injuries resulting from seizures in 2 separate patients (clavicle fracture, head laceration requiring closure). There were no SAEs of falls reported.

- Psychotic Disorders
  No psychotic disorders were reported in the safety population.

- DRESS/ Multi-organ Hypersensitivity
  No possible cases of DRESS were identified in the safety population.

- Memory impairment, amnesia, and cognition
  Two subjects reported a TEAE of memory impairment, and one subject reported questionable “amnesia”, all of which were considered nonserious and did not lead to discontinuation. There were no reported AEs of cognitive disorder.

- Seizure-related TEAEs
  Seizure events were recorded as TEAEs if there was a change in seizure type or exacerbation in the seizure activity (frequency, severity or duration). Seizure-related TEAEs were differentiated from investigator and parent judgment of lack of efficacy. Thirty-one subjects reported convulsion as a TEAE, and 11 of those had concurrent TEAEs that may have lowered seizure threshold (infection, pyrexia, GI related illnesses that may decrease absorption).

  Status epilepticus occurred in seven subjects, all of which were SAEs, but none resulted in discontinuation of medication. Only four subjects discontinued medication due to convulsion, and those were not SAEs.

Other seizure-related terms were used for change in seizure type/intensity such as partial seizures, partial seizures with secondary generalization, and intractable epilepsy.

- Pediatric Growth, Neurodevelopment, Behavior, and Endocrine-related TEAES
  The following neurodevelopment and behavior terms were all reported in (n) subjects: Learning disorder (1), psychomotor retardation (1), abnormal behavior (6), aggression (10), ADHD (1), attention disturbance (2), impulsive behavior (2), irritability (10), personality change (1), emotional disorder of childhood (1), and psychomotor hyperactivity (3). See further discussion of these behavior terms in Section 7.4.1. Also, note that aggression and irritability are already labeled adverse events.

  There were three subject who had a TEAE of weight increased, and five subjects with a TEAE of weight decreased. There were no clinically significant endocrine-related TEAEs.

Reviewer's comment: The specified areas of interest were appropriate based on the known prescribing information and current Warnings and Precautions, as well as the safety population. There were no new safety concerns identified in these analyses

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The following table (Table 11) illustrates the incidence of all adverse events reported in ≥ 2% of the safety population of subjects age 4 years and over after recoding (see Table 3). Overall, the common adverse events were quite similar in quality to those noted in the adult studies, however differences in study design and study duration make it hard to make direct comparisons to incidence rates in the labeled adult studies. Furthermore, the lack of placebo-controlled data makes it difficult to reach significant conclusions about new safety signals.

Table 11: TEAEs reported in ≥ 2% of the safety population

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

Source: Clinical reviewer's analysis of the Pool SPX-1 data of Subjects over age 4 years

The following adverse events were reported in > 10% of the population: vomiting (17.4%), dizziness (16.5 %), somnolence (12.8%), and headache (12.2%), all of which are reported as common adverse events in the controlled studies of the adult population.

Furthermore, nasopharyngitis, pyrexia, and upper respiratory tract infection are also reported in > 10% of the safety population, all of which occur frequently in pediatric subjects and did not appear related to the medication.

Finally, seizures of all types were reported as an adverse event in 11.6 %, indicating either a change in seizure type or worsening of severity or frequency, but the lack of placebo data makes it hard to know if this is typical for this highly refractory pediatric epilepsy population.

Analysis of other common adverse events for possible safety signals

Vomiting: As noted above, vomiting was a commonly reported TEAE with an incidence of 17.4% in the safety population, which is already in the prescribing information. Although it is also noted in the adult studies at a slightly lower incidence of 9%, it is hard to directly compare incidence rates for reasons noted above. Furthermore, children in general are more likely to have vomiting unrelated to the medication (viral illness, gastroenteritis) and I cannot control for these factors given the lack of controlled data. The narratives of the events of vomiting that were reported as SAEs or led to discontinuation were reviewed and the majority were confounded by underlying viral illness, associated seizures, or other concurrent gastrointestinal complaints.

Abdominal pain/decreased appetite: Abdominal pain, once recoded with the similar terms abdominal pain upper and abdominal discomfort, resulted in an almost 10% (9.6%) incidence of abdominal pain in the safety population. However, abdominal pain as an AE is often accompanied by concurrent vomiting and/or nausea, which are both

already in the prescribing information and it is, therefore, not significantly different enough to be considered a new safety concern.

Additionally, (b) (4) . However, it is commonplace for young children to experience decreased appetite in the context of higher rates of vomiting, nausea, and abdominal pain. Some of the reports of decreased appetite were in the setting of tonsillitis and pharyngitis, which is an expected associated finding. Given that the only data for review was open-label data, although there were a few cases of isolated decreased appetite, I do not recommend inclusion in the label as a new signal. Further analysis will be completed when full datasets are submitted from the controlled pediatric study (Study 0969).

Dizziness and ataxia: Dizziness and ataxia are already listed in the Warnings and Precautions section of the prescribing information due to high incidence in adult studies. In the pediatric safety population, 54 subjects (16%) reported dizziness. Ataxia was only reported in 4 subjects (1.2%); however, if you combine preferred terms of balance disorder, gait disturbance (verbatim term of unsteady gait), and coordination abnormal, which are all similar terms, especially in pediatric subjects, then there was an incidence of 6% in the safety population.

Lethargy: (b) (4) Upon further review, it is noted that somnolence and other fatigue-related AEs, when taken together, were reported in 24% of the safety population, which includes the terms somnolence, sedation, fatigue, lethargy, malaise, asthenia and hypersomnia. While difficult to compare to prior adult studies as noted above, this incidence appears similar to the incidence of fatigue-related AEs that were reported in the adult population. Three of these events of lethargy led to discontinuation, and two subjects experienced SAEs; however, these were confounded by other associated symptoms and diagnoses and the SAEs appeared unrelated to the medication, thus, the incidence of lethargy did not raise a concern for a new safety signal. Furthermore, I feel that lethargy is not distinct enough from somnolence and fatigue, both of which are listed as adverse reactions from the adult controlled data, to warrant separate mention in the prescribing information.

Abnormal behavior: (b) (4) However, the incidence of psychiatric comorbidities is high at baseline in the pediatric epilepsy population; therefore, it is difficult to determine if there is a safety signal based on the open-label data in this submission. Additionally, I reviewed the verbatim terms that were coded as abnormal behavior and found the terms to be vague (“subdued”, “touchy behavior”,

"behavior problems") and to not clearly fall into a diagnostic category. Therefore, I do not recommend inclusion of "abnormal behavior" in the label.

Given the concerns for exacerbation of behavioral problems with AEDs in general, I reviewed the broader group of "behavior-related terms" to determine if there was a safety signal for VIMPAT. The following terms were reported: Learning disorder (1), psychomotor retardation (1), abnormal behavior (6), aggression (10), ADHD (1), attention disturbance (2), impulsive behavior (2), irritability (10), personality change (1), emotional disorder of childhood (1), and psychomotor hyperactivity (3). The most common terms, aggression and irritability, are already in the label for VIMPAT. Psychomotor hyperactivity was reported in 3 subjects, all for the verbatim terms of "worsening hyperactivity", and the related term "ADHD" was for worsening of a pre-existent diagnosis. As hyperactivity and ADHD are again quite frequent in both this age group (4-9 years) and in patients with childhood epilepsy, the lack of controlled data again make it difficult to determine the significance of these few cases. The remaining terms did not occur in sufficient number to suggest a new signal. Of note, some of these terms were also reported together in the same patients.

Overall, the incidence of psychiatric disorder adverse events was 16.1%, many of which were related to above-mentioned behavior changes. Although differences in study design limit our ability to directly compare incidence rates between the adult and pediatric populations, I would have expected a somewhat higher incidence in the pediatric studies, given the open-label study design and longer duration. However, this incidence of psychiatric TEAEs in pediatric subjects overall is quite similar to the incidence of psychiatric TEAEs seen in the adult POS population (17%), reassuring that there is less likely a signal unique to pediatric patients.

(b) (4)

Additionally, the final study reports from the open-label extension studies SP848 and EP0034, which will include data from the Child Behavior Checklist, will be reviewed upon their submission at the conclusion of those studies.

Reviewer's note: The common adverse event listing in the open-label pediatric population did not vary significantly enough from adult population to raise any new safety concerns. Overall, the most frequent common adverse events were consistent with those seen in adult subjects.

7.4.2 Laboratory Findings

The laboratory findings were reviewed from each study independently, and there was no evidence of any new safety concerns in the laboratory findings.

A few isolated patients had an increase in AST/ALT > 2x ULN, but no one had elevated bilirubin, no one met criteria for Hy's law, and many subjects with elevated GGT had elevations at baseline as well with no shift after starting treatment. There were no TEAEs related to elevated liver function tests reported. Elevated liver enzymes are described in the label.

No other clinically significant lab shifts or patterns were identified.

7.4.3 Vital Signs

Vital signs (Mean SBP, DBP and pulse rate) were analyzed by mean change from baseline for each study, and vital signs were also reviewed for markedly abnormal values. The majority of the vital sign mean changes from baseline noted throughout the studies were small and not clinically relevant. An isolated event of bradycardia is described above under significant adverse events (Section 7.3.5). Weight, height and BMI were also analyzed as mean change from baseline. There was a single report of a SAE of decrease in weight in one subject, which was mild in severity, associated with multiple comorbid conditions, and did not lead to discontinuation.

Of note, in the analysis of the 15 subjects less than 4 years of age, there was one event of decreased weight that was severe in intensity. There was also a slightly increased mean change in pulse rate in subjects under age 4 compared with older age groups. However, given the small number of subjects, and the fact that pulse rate physiologically decreases more in younger children as they get older, the significance of this is unclear at this time.

7.4.4 Electrocardiograms (ECGs)

There were few ECG changes that were felt to be of clinical significance, but no serious changes were noted in any subjects. There was a noted increase in PR duration that was consistent throughout all age groups, weight groups and studies, and was similar to that seen in adult subjects. (see also Section 4.4.2)

The following ECG abnormalities as adverse events were also reported (*see also* Section 7.3.5):

- An 11-year-old subject developed an intraventricular conduction delay that was mild, non-specific, and associated with sinus arrhythmia, which resolved spontaneously without discontinuation.
- A 10-year-old subject developed first-degree AV block at week 4 with no past medical history of cardiac abnormalities, however his baseline ECG was also abnormal and did not lead to drug discontinuation.
- A 6-year-old subject had QT prolongation while taking 10 mg/kg/day. The QT prolongation noted was mild, not serious, but did lead to discontinuation.

Symptoms resolved upon withdrawal of the drug. He did have a history of cardiac arrhythmia previously (see Section 7.3.3).

- A 12-year-old subject had moderate QT prolongation that did not lead to discontinuation of the drug.
- A 7-year-old subject was reported to have bundle branch block on ECG that was considered mild and not felt to be related to the study drug by the investigator.

Reviewer's comment: VIMPAT prescribing information lists cardiac conduction and rhythm abnormalities in Warnings and Precautions. The findings here are compatible with the current label, and I did not identify any new safety signals.

7.4.5 Special Safety Studies/Clinical Trials

There were no special studies performed in renal or hepatic impairment in pediatric subjects.

Studies were completed previously in adults with renal impairment. Based on adult data as well as the population PK studies, it was determined that no dose adjustment is necessary in pediatric subjects with mild to moderate renal impairment. However, pediatric subjects with severe renal impairment (Cr_{Cl} < 30 ml/min/1.73 m^2 as estimated by the Schwartz equation) or end-stage renal disease should have a reduction of 25% of their maximum dose. These recommendations are consistent with recommendations in adult patients.

Recommendations for pediatric subjects with hepatic impairment are also based on previous studies in adults, as well as the population PK data. The recommendations are to reduce the dose 25% in subjects with mild to moderate hepatic impairment, and to avoid drug administration completely in severe hepatic impairment.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Overall, the majority of adverse events were independent of dose. However, there were some notable patterns at higher doses. The incidence of vomiting was notably higher at higher doses. The incidence of pyrexia was also highest in the 12 mg/kg/day modal dose category, however, pyrexia was also higher in the < 30 kg weight group, who tended to require higher doses in general. Convulsion was also highest in the > 12 mg/kg/day group, likely due to the underlying severity of disease in these subjects requiring higher doses of medication.

7.5.2 Time Dependency for Adverse Event,

Many of the TEAES were within the first 3 months of treatment and 6% of treatment emergent SAEs occurred during first 3 months of treatment. However, prior exposure from the earlier double-blind study for subjects in EP0034 was not taken into consideration in the time dependency evaluations so total time exposed to drug at the time the adverse event occurred is unknown.

7.5.3 Drug-Demographic Interactions

Review of the data found no gender-specific differences in incidence or severity of adverse events. There was no race-based safety signal identified.

7.5.4 Drug-Disease Interactions

No specific drug-disease interactions were noted.

7.5.5 Drug-Drug Interactions

No new drug-drug interaction studies were performed in pediatric subjects, although they were previously performed for the initial NDA in adults. The applicant did conduct covariate analyses as part of the PK modeling and simulation report, and found that administration of hepatic enzyme-inducing AEDS (carbamazepine, phenytoin, and phenobarbital) increased LCM clearance.

In previously studied adult drug-drug interactions, giving LCM with enzyme inducers decreased the overall systemic exposure of LCM by 25%. LCM has both broad safety and efficacy margins, and therefore, dosage adjustments are deemed unnecessary. See Clinical Pharmacology review for further details.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No studies were required for this supplement.

7.6.2 Human Reproduction and Pregnancy Data

No new studies were completed. Literature was reviewed by DPMH and the nonclinical and safety review team to support revisions to the pregnancy and lactation section of the label to update it to PLLR format.

7.6.3 Pediatrics and Assessment of Effects on Growth

The effects in pediatric subjects and on growth are the main subject of this review. See also Section 7.3.5 and Section 7.4.3.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overall, there were two subjects in the study who had accidental overdose of LCM.

- An 11-year-old (SP0848-061-10794) presented with vomiting, partial seizures, and an ECG abnormality with intraventricular conduction delay after accidental overdose of LCM. Symptoms were mild, did not lead to discontinuation, and resolved on the same day.
- A 15-year-old female (SP0847-012-00024) had symptoms of overdose with dizziness, disorientation, gait disturbance and vomiting. The symptoms were moderate, resolved the same day, and did not lead to discontinuation.

These events are consistent with those currently described in the overdose section of the label.

As part of the study, 16 subjects were also prescribed doses > 12 mg/kg/day, and four of these subjects received doses of 15 mg/kg/day in tablet form. Only one of these subjects receiving over 12 mg/kg/day had a related TEAE (vomiting).

LCM is currently a Schedule V controlled substance. Throughout the study, there were no reports of euphoria or any TEAEs related to drug withdrawal syndrome. There are no proposed changes to the Schedule classification or dependence information.

7.7 Additional Submissions / Safety Issues

In May 2017, a 120-day safety update was submitted which included a summary of pediatric subjects and new adverse events reported in the 120 days following the initial clinical cutoff date in the ongoing studies (SP848 and EP0034). Furthermore, along with that submission was an analysis of all incidents of DRESS, falls, and injuries since August 1, 2013 in all VIMPAT studies (adult and pediatric), as well as mention of all deaths and SAEs in all ongoing VIMPAT studies.

The pediatric safety update revealed two new deaths which are summarized above in Section 7.3.1. There was no increase in the incidence of SAEs or severe TEAEs in the safety update, and the percentage of subjects who experienced the TEAE of status epilepticus and the TEAE of convulsion decreased. There were two additional subjects with ECG abnormalities but they were not serious and did not lead to discontinuation. Additionally there were a few additional positive responses to suicidal screening, but no

further suicide attempts. There were no additional reports of euphoria or withdrawal/rebound symptoms.

There were no pediatric cases of DRESS (Multi-organ hypersensitivity) reported. There were several falls and injuries reported, but most did not appear related to the drug itself and about half of them were associated with concurrent seizures.

There were three possible cases of DRESS reported in adult subjects since August 1, 2013, with no associated deaths.

The final study report from SP0969, a placebo-controlled, double-blind study of treatment of partial onset seizures in pediatric patients age 4 to < 17 years was submitted to INDs 057939/073809 during the course of this review. The datasets were not submitted for review to this sNDA, but a high-level review of the completed study report revealed no new safety concerns.

Reviewer's comment: The 120-day safety update did not raise any new safety concerns. The final study report for SP0969 also did not introduce any new safety concerns, although the data was not reviewed.

8 Postmarket Experience

As noted, LCM was approved in October 2008 as adjunctive therapy in treatment of POS in patients 17 years of age and older. Using a data lock of May 2, 2016, the applicant submitted postmarketing data regarding off-label use of LCM in patients under 18 years of age. The data submitted is based on a search of the UCB Global Safety database for all postmarketing cases compatible with use in the pediatric population. All reports of use in patients under 17 years of age are recorded in the database, whether or not there was an accompanying adverse event.

The applicant's global safety database 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. The cases submitted include cases reported in literature but excludes any cases from clinical trials.

Of the 1077 cases in patients age 4 to < 17 years, 16% of AEs were reported as serious, and there were 14 (1%) deaths. Some of the data was limited or had sparse details. Overall, the data reviewed did not reveal any new safety concerns.

The following table (Table 12) presented by the applicant includes the most frequently reported PTs in patients age 4 to < 17 years, which are all adverse events that are already expected and reported in the current prescribing information. The "wrong

technique in product usage process" refers mostly to crushing of the tablet or administering LCM through a feeding tube.

Weight increased, reported as a frequent complaint in 25 subjects, was not noted as a safety signal in the pooled safety data from the adult and pediatric clinical studies. Weight increased was also refuted as a safety signal in 2013, based on a comprehensive review of the adult data as part of a formal safety signal assessment report (SSAR).

Table 12: Postmarketing frequently reported PTs (≥20) in patients 4 to < 17 years of age

MedDRA PT	Event PT Count (total = 1843)[a]
No adverse event[b]	419 (23%)
Ineffectiveness (Drug ineffective and Drug ineffective for approved indication)	136 (8%)
Seizure	118 (6%)
Dizziness	42 (2%)
Fatigue	36 (2%)
Nausea	33 (2%)
Vomiting	33 (2%)
Somnolence	26 (1%)
Aggression	26 (1%)
Wrong technique in product usage process	25 (1%)
Weight increased	25 (1%)
Abnormal behavior	22 (1%)

MedDra = Medical Dictionary for Regulatory Activities; PT = preferred term
[a] More than one event can be reported for the same patient
[b] No adverse event is the PT used when no clinical events were associated with drug exposure
[c] Percentages are based on the total number of PTs
Copied from Applicant's submitted Appendix 1, Table 2-3

Of note, in the population under age 4, there were five deaths, 21% SAEs, and a few individual reports of decreased appetite (3). Of the 7,524 adult patients, the common AEs were consistent with the current prescribing information.

Table 13 presents the postmarketing cases by topic of interest, in patients 4 to < 17 years of age.

Table 13: Overview of postmarketing analysis for patients age 4 to < 17 years

Topics of interest	No. of cases in pediatric patients 4 to < 17 N=1077 (%)
Cases with fatal outcome	14 (1.3%)
Cardiac/ECG-related events	26 (2.4%)
Syncope and LOC	3 (0.2%)
Suicidality-related events	8 (0.7%)
Hepatotoxicity-related events	4 (0.4%)
Dizziness and ataxia	41 (3.8%)
Worsening of seizure	66 (6.1%)
Lack of efficacy	130 (12.1%)
Multi-organ hypersensitivity and SCARs	6 (0.5%)
Potential LCM long term effects	12 (1.1%)

Adapted from Applicant's Appendix 1, Table 2-10

The cases associated with these search terms were reviewed in detail and there was no new safety signal identified. Although some cases had poor documentation, all of the cases were consistent with known risks already described in the prescribing information.

Of the 14 deaths, three were cases of probable SUDEP but there was no indication that the LCM causally increased the risk of SUDEP. The other deaths were mostly due to underlying illness, or there were multiple confounders and concomitant medications with no evidence of causality of LCM in any of the cases.

Sixty-six patients reported potential worsening of their seizures, none of which were fatal. Twenty-one of these cases had a positive dechallenge, however, there were multiple confounding variables including concurrent withdrawal of other AEDs during LCM titration, as well as progression of underlying illness. There was no pattern indicating LCM as the cause of seizure worsening.

The postmarketing data revealed four cases that met criteria for Multi-organ Hypersensitivity (DRESS), but there was not enough data to support causality. Additionally, there were also two reported cases of Stevens-Johnson syndrome.

There was no evidence of drug abuse, although there were two reported cases of euphoric mood. There were multiple reports of neurodevelopmental changes, including 22 patients reporting abnormal behavior, as well as a few reports each of agitation and irritability.

Reviewer's note: The complete postmarketing data was reviewed and no new safety signals were identified. Overall, adverse events reported from the off-label

use of commercially available LCM were consistent with both those seen in the clinical study safety population, and those adverse events seen in adults.

9 Appendices

9.1 Literature Review/References

1. Men A, Mehrotra S, Bhattaram A et al. Full extrapolation of efficacy from adults to children of antiepileptic drugs indicated for the treatment of partial onset seizures: a scientific and regulatory perspective. Annual Meeting of American Epilepsy Society 2016: Abstract 1.075.
2. Pellock JM, Arzimanoglou A, D'Cruz O et al. Extrapolation evidence of antiepileptic drug efficacy in adults to children > 2 years of age with focal seizures: the case for disease similarity. Epilepsia 2017. doi: 10.1111/epi.13859
3. VIMPAT® (lacosamide). Prescribing Information, UCB Inc: March 2017.

9.2 Labeling Recommendations

Based upon the findings of this review, revisions to the label are suggested for Sections 2 Dosage and Administration, Section 6 Adverse Reactions, Section 8.4 Pediatric Use, and Section 14 Clinical Studies. Please see final approved labeling.

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/s/

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10/24/2017

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11/02/2017