CLINICAL REVIEW

Application Type	NDA efficacy supplement
Application Number(s)	022253 (S-49) / 022254 (S-39) / 022255 (S-31)
Priority or Standard	Standard
Submit Date(s)	12/15/2020
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Division/Office	Division of Neurology 2/ Office of Neuroscience
Reviewer Name(s)	Emily R. Freilich, MD
Review Completion Date	9/29/2021
Established/Proper Name	Lacosamide
(Proposed) Trade Name	Vimpat
Applicant	UCB, Inc
Dosage Form(s)	Oral tablet, oral solution, injection for intravenous infusion
Applicant Proposed Dosing Regimen(s)	Recommended dosage is based on body weight for pediatric patients
Applicant Proposed Indication(s)/Population(s)	For treatment of partial-onset seizures (POS) in patients 1 month and older (all formulations)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For treatment of partial-onset seizures (POS) in patients 1 month and older

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Glossary

AC	advisory committee
AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BRV	brivaracetam
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
EEG	electroencephalogram
ETASU	elements to assure safe use
EU	European Union
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GRMP	good review management practice
HR	heart rate

ICH	International Council for Harmonization
IDMC	independent data monitoring committee
IGE	idiopathic generalized epilepsy
IIL	initiating initial lacosamide patient population
ILAE	International League Against Epilepsy
IMP	investigational medicinal product
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
LCM	lacosamide
LEV	levetiracetam
LFT	liver function test
MAO-I	monoamine oxidase A
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OLL	open-label lacosamide patient population
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PDILI	potential drug-induced liver injury
PGTCS	primary generalized tonic clonic seizures
PHT	phenytoin
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PO	oral
POS	partial-onset seizures
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report

PT	preferred term
REMS	risk evaluation and mitigation strategy
RxL	prescribed lacosamide patient population
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
SPA	Special Protocol Assessment
SUDEP	sudden unexpected death in epilepsy patients
TEAE	treatment emergent adverse event
ULN	upper limit of normal
VNS	vagal nerve stimulator
VPA	valproic acid
WRO	written response only

1. Executive Summary

1.1. Product Introduction

Lacosamide (LCM), a slow sodium channel antagonist, is currently approved for the treatment of partial-onset seizures (POS) and primary generalized-tonic-clonic seizures (PGTCS) in patients 4 years and older for all formulations. LCM is believed to exert its antiepileptic effect through selectively enhancing slow inactivation of voltage-gated sodium channels, thereby increasing activation thresholds, and leading to reduction of neuronal hyperexcitability.

LCM was approved in 2008 for the adjunctive treatment of POS in adults 17 years and older in both oral and intravenous formulations; the oral solution was added in 2010, and the use of a loading dose and monotherapy for the treatment of POS in adults were added in 2014. The indication for the treatment of POS was extended down to 4 years of age in 2017 for oral formulations only. In 2020, LCM was approved for adjunctive treatment of PGTCS in patients 4 years and older, and the intravenous formulation was approved for pediatric patients 4 years and older for treatment of both POS and PGTCS.

The current supplement intends to extend the indication for the treatment of POS down to 1 month of age for all formulations (oral tablet, oral solution, and intravenous formulation).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The effectiveness of LCM for the treatment of POS in pediatric patients ≥ 1 month to less than 4 years of age is established through extrapolation from adult and older pediatric data with supportive clinical pharmacology pediatric pharmacokinetic (PK) data in this age group.

In 2015, the Division initially determined that pediatric extrapolation from adult data could be used to support evidence of effectiveness in the treatment of partial onset seizures in pediatric patients 4 years and older. This was subsequently determined to be acceptable down to 2 years of age, and most recently down to 1 month of age. This determination was communicated to the Applicant in Type C WRO Meeting Responses dated November 30, 2020.

In a subsequent General Advice letter dated February 26, 2021, the Division outlines the basis for the acceptance of pediatric extrapolation in the treatment of partial-onset seizures and the requirements necessary to support such an indication in the age group 1 month to less than 4 years. The following are required to support an indication for the treatment of POS in patients 1 month and older that relies upon extrapolation:

- Approved indication for the treatment of POS in adults

- A pharmacokinetic analysis to determine the dosing regimen that provides similar drug exposure (at levels demonstrated to be effective in adults) in pediatric patients 1 month of age and older and in adult patients with POS. This analysis will require pharmacokinetic data from both the adult and pediatric populations.
- Long-term, open-label safety study(ies) in pediatric patients 1 month of age and older.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The overall benefit-risk analysis of VIMPAT for treatment of partial-onset seizures (POS) in pediatric patients down to 1 month of age is acceptable. Pediatric patients with epilepsy often have refractory seizures that are difficult-to-treat and do not respond to currently available medications. Untreated seizures increase the risk for status epilepticus and sudden death in epilepsy patients (SUDEP) and may increase the risk of neurocognitive and neurobehavioral co-morbidities and developmental delays. Despite the use of currently approved therapies, often as polypharmacy, many children continue to experience frequent seizures and require additional medication options.

The Division recently determined that extrapolation is appropriate for treatment of POS down to age 1 month, based on similar pathophysiology of POS in both adults and children, as well as a review of several marketed antiepileptic drugs showing similar exposure-response relationships in both adults and older pediatric patients with POS. LCM was previously approved as VIMPAT in the United States in 2008 for the treatment of partial-onset seizures in adults in both oral tablet and intravenous formulations. The oral solution was approved in 2010. The oral formulations were extended down to patients age 4 years and older in 2017 using pediatric extrapolation to demonstrate evidence of effectiveness. The intravenous formulation was approved in pediatric patients down to age 4 years in 2020. The Applicant has a PREA post-marketing requirement (PMR) to study the efficacy, safety, and pharmacokinetics (PK) of in the treatment of POS in patients 1 month to less than 4 years of age for each formulation.

The safety of VIMPAT is well-characterized in adults, and common adverse events noted in pediatric patients 4 to less than 17 years of age were similar to those seen in adults. The Applicant has submitted safety data from a randomized, double-blind, placebo-controlled safety and efficacy study in 255 pediatric patients age greater than or equal to 1 month to less than 4 years, as well as open-label, long-term safety data on the same population, and no new safety signals were identified. The adverse events were similar to those seen in adults and older pediatric patients. An open-label safety and tolerability study of the intravenous formulation of VIMPAT provides data on an additional 26 patients in this population of pediatric patients greater than or equal to 1 month to less than 4 years of age.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Partial-onset seizures in pediatric patients may be refractory and difficult to treat. • Refractory seizures increase the risk of life-threatening conditions such as status epilepticus, as well as the risk for sudden death. • Uncontrolled seizures also put the child at risk for neurodevelopmental delays and cognitive impairment. • Despite polypharmacy with current approved treatments, many pediatric patients continue to have frequent seizures.	There is continued need for new, approved medications in very young patients with partial-onset seizures.
Current Treatment Options	• The only medications approved for the treatment of POS in patients less than 4 years of age include levetiracetam, lamotrigine, topiramate, oxcarbazepine, gabapentin, pregabalin, and valproic acid. • Of those, only levetiracetam and pregabalin are approved in patients less than 2 years of age.	Most treatments used in this age group are off-label, unapproved use of medications approved for adults. There is a need for approved drugs with adequate PK, safety, and dosing information to help providers choose appropriate treatment in this age group.
Benefit	• Lacosamide reduces seizure frequency in adults and older pediatric patients with partial-onset seizures.	Efficacy is based on extrapolation of dose-exposures in the adult population to that of the young pediatric population age 1 month to less than 4 years of age.
Risk and Risk Management	• The safety profile of LCM is well-characterized in adults and older pediatric patients. • The controlled and open-label safety data of LCM in 255 pediatric patients greater than or equal to 1 month to less than 4 years of age did not reveal any new safety signals. • The most common adverse events were somnolence and vomiting.	LCM was well-tolerated by pediatric patients age 1 month to less than 4 years of age. There were no new safety signals identified, and the adverse event profile is expected to be similar to that seen in adults and older pediatric patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The safety of intravenous LCM in 26 pediatric patients greater than or equal to 1 month to less than 4 years of age was similar to that in pediatric patients greater than 4 years of age.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

The Applicant proposes expansion of the current indication for the treatment of POS in patients 4 years of age and older down to 1 month of age, based on the use of pediatric extrapolation, with the accompanying safety and PK data. Epilepsy is a common neurological disease characterized by recurrent seizures, which are classified by their electrical and clinical features. Epilepsy affects individuals of all ages and is one of the most common neurologic disorders in all age groups. A large meta-analysis of population-based epilepsy studies found the point prevalence of epilepsy to be 6.38 per 10000, the lifetime prevalence 7.6 per 1000, annual cumulative incidence of 67.77 per 100,000 persons, and an incidence rate of 61.44 per 100,000 person-years.[1] In an analysis based on health insurance claims, the incidence and prevalence estimate of epilepsy in the US pediatric population in 2012 were 6.8 per 1000 and 104 per 100,000 children, respectively[2]. Although 8 to 10% of the population will experience a seizure during their lifetime, only 2 to 3% will go on to develop epilepsy[3]. Partial-onset seizures occurred in ~57% of patients with epilepsy assessed over a 50-year period in Rochester, MN[4], and ranges from 12% to 71% in a variety of published epidemiological studies, depending on diagnostic criteria and country being assessed[5].

Uncontrolled partial-onset seizures are associated with poorer quality of life because of a variety of limitations (e.g., inability to drive, social isolation, difficulty maintaining employment), and also can cause significant adverse consequences, including severe trauma, depression, anxiety, and sudden death.[6,7]. Uncontrolled epilepsy in the pediatric patients, especially in those patients with an earlier age of seizure onset, is also associated with developmental delays

[1] Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy A systematic review and meta-analysis of international studies. Neurology 2017:88; 296-303
[2] Kim H, Thurman DJ, Durgin T, et al. Estimating Epilepsy Incidence and Prevalence in the US Pediatric Population Using Nationwide Health Insurance Claims Data. J Child Neurology 2016, Vol. 31(6) 743-749
[3] Gavvala JR and Schuele SU. New-Onset Seizure in Adults and Adolescents A Review. JAMA. 2016;316(24):2657-2668
[4] Hauser WA, Annegers JF, Rocca WA. descriptive epidemiology of epilepsy: contributions of population-based studies from Rochester, Minnesota. Mayo Clin Proc. 1996 Jun;71(6):576-86.
[5] Banerjee PN, Filippi D, Hauser WA. The descriptive epidemiology of epilepsy—a review. Epilepsy Res. 2009 Jul;85(1):31-45.
[6] Baranowski CJ. The quality of life of older adults with epilepsy: A systematic review. Seizure. 2018 Aug;60:190-197.
[7] Sadr SS, Javanbakht J, Javidan AN, et al. Descriptive epidemiology: prevalence, incidence, sociodemographic factors, socioeconomic domains, and quality of life of epilepsy: an update and systematic review. Arch Med Sci. 2018 Jun;14(4):717-724

and worse neurocognitive outcomes.[8] Focal or partial-onset seizures involve only a portion of the brain at the onset, originating in one or more localized foci. Seizures that originate focally and spread to involve the majority or entirety of the brain are a subset of focal seizures, called secondarily generalized seizures[9]. Recently proposed terminology by the International League Against Epilepsy (ILAE) has redefined POS as "focal seizures" with a variety of seizure subtypes: focal aware seizures, focal impaired awareness seizures, focal motor seizures, focal non-motor seizures, and focal to bilateral tonic–clonic seizures[10]. The term POS will be used throughout this review. Partial or focal seizures may begin with motor, sensory, autonomic, or psychic symptoms, depending on the location of the electrical discharge[11].

2.2. Analysis of Current Treatment Options

A total of 16 drugs are approved for use in the treatment of POS in pediatric patients with varying degrees of supporting efficacy data.
Table 1 below summarizes the currently approved drugs that have clearly-defined indications for use in pediatric patients with POS and efficacy data to support the claims. Other drugs not listed here that are also used to treat pediatric patients with POS include phenobarbital, primidone, phenytoin, carbamazepine, vigabatrin, and felbamate. These are not included in the table because of lack of clear pediatric indications, lack of NDA approval, or contraindication for use as first-line treatment due to adverse drug effects.

Of the below drugs listed in Table 1, the only drugs approved for patients younger than 4 years of age:

- levetiracetam (1 month of age and older)
- lamotrigine, topiramate, and oxcarbazepine (2 years of age and older)
- gabapentin (3 years of age and older)
- pregabalin (1 month of age and older)
- valproic Acid (age not specified)

Table 1 Summary of Drugs Currently Approved for Treatment of Partial-Onset Seizures in Pediatric Patients

[8] Nickels KC, Zaccariello MJ, Hamiwka LD, Wirrell EC. Cognitive and Neurodevelopmental Comorbidities in Paediatric Epilepsy. Nat Rev Neurol. 2016 Aug; 12(8):465-476.
[9] Scheffer IE, Berkovic S, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017 Apr; 58(4):512-521
[10] Fisher RS. The New Classification of Seizures by the International League Against Epilepsy 2017. Curr Neurol Neurosci Rep (2017) 17: 48
[11] Chang BS and Lowenstein DH. Mechanisms of Disease: Epilepsy. NEJM (2003) 349;13

Product (s) Name	Relevant Pediatric Indication	Year of Pediatric Approval	Route and Frequency of Admin.	Efficacy Information	Important Safety and Tolerability Issues

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Product (s) Name	Relevant Pediatric Indication	Year of Pediatric Approval	Route and Frequency of Admin.	Efficacy Information	Important Safety and Tolerability Issues
Brivaracetam* (BRV)	Treatment of partial-onset seizures in patients 4 years of age and older **Brivaracetam was recently approved for the treatment of POS in patients 1 month and older on August 30, 2021*	2018	PO/IV, BID Weight-based dosing pediatric pts	Adjunctive and monotherapy use approved in pediatric population based on extrapolation of efficacy from adult studies using pediatric PK data, as well as adequate pediatric safety data.	Adverse reaction in pediatric patients similar to those seen in adults. Warnings: Neurological Adverse Reactions (somnolence and fatigue, dizziness and disturbance in gait and coordination), Psychiatric Adverse Reactions (including aggression, anger, agitation, depression, hallucination, paranoia, acute psychosis, and psychotic behavior), bronchospasm and angioedema.
Eslicarbazepine (ESL)	• Treatment of partial-onset seizures in patients 4 years of age and older	2017	PO, QD Weight-based dosing ages 4-17 yrs	Adjunctive and monotherapy use approved in pediatric population based on extrapolation of efficacy from adult studies using pediatric PK data, as well as adequate pediatric safety data.	Pediatric safety data not significantly different from adult data. Warnings: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), DRESS, anaphylaxis and angioedema, hyponatremia, dizziness, gait/coordination disturbance, somnolence/fatigue, cognitive dysfunction, impaired vision, DILI

Product (s) Name	Relevant Pediatric Indication	Year of Pediatric Approval	Route and Frequency of Admin.	Efficacy Information	Important Safety and Tolerability Issues
Gabapentin (GBP)	Adjunctive therapy in the treatment of partial onset seizures, with and without secondary generalization, in adults and pediatric patients 3 years and older with epilepsy	2000 (adjunctive use in pediatric POS)	PO, TID Weight-based dosing for patients 3-11 years of age	Placebo-controlled efficacy trial in 247 pediatric patients with POS. Comparison of response ratio to placebo statistically significant (-0.146 vs -0.079) but responder rate not significantly different frequency)	Somnolence and sedation, dizziness, DRESS In pediatric patients: Neuropsychiatric Adverse Reactions (emotional lability, hostility and aggression, concentration issues, and hyperkinesia
Lacosamide (LCM)	Treatment of partial-onset seizures in patients 4 years of age and older	2017	PO or IV, BID Weight-based dosing pediatric pts <50 kg	Adjunctive and monotherapy use approved in pediatric population based on extrapolation of efficacy from adult studies using pediatric PK data, as well as adequate pediatric safety data.	Adverse reaction in pediatric patients similar to those seen in adults. Warnings: dizziness and ataxia, cardiac rhythm, and conduction abnormalities (prolonged PR, Atrial fibrillation, and Atrial flutter), syncope, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS),
Lamotrigine (LTG)	Adjunctive therapy in patients aged 2 years and older: • partial-onset seizures. • primary generalized tonic-clonic seizures. • generalized seizures of Lennox-Gastaut syndrome. Monotherapy in patients ≥16 years of age only.	2003 (pediatric adjunctive POS)	PO, BID Weight-based dosing for patients 2-12 years of age	Placebo-controlled efficacy trial in 199 patients aged 2 to 16 years. Primary efficacy endpoint: percentage change from baseline in all partial-onset seizures. The median reduction of all POS was 36% in patients treated with LAMICTAL and 7% on placebo (P<0.01).	Serious skin rash, including in pediatric patients (one death in controlled pediatric trials), TEN. Significant rash with concurrent valproate. Hemophagocytic Lymphohistiocytosis, DRESS, hematologic abnormalities (neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia), Aseptic Meningitis,

Product (s) Name	Relevant Pediatric Indication	Year of Pediatric Approval	Route and Frequency of Admin.	Efficacy Information	Important Safety and Tolerability Issues
Levetiracetam (LEV)	Adjunctive therapy in the treatment of: • POS in patients one month of age and older with epilepsy PGTCS in patients 6 years of age and older with idiopathic generalized epilepsy	2000 (4-17 years) 2012 (1 mo to 4 years) 2014 (IV)	PO/IV, BID Weight-based dosing in ped patients	1 mo to 4 yrs: RPCT evaluating the efficacy and tolerability in patients with refractory POS. Primary endpoint was responder rate, with statistically significantly greater number of responders on Keppra than on placebo	Warnings: Behavioral abnormalities and psychotic symptoms, somnolence and fatigue, anaphylaxis and angioedema, SJS and TEN, coordination difficulties, reduction in WBC and neutrophil counts (statistically sig worse in Keppra-treated pediatric patients than those on placebo), hypertension (particularly in the 1 mo to 4 yr study)

Product (s) Name	Relevant Pediatric Indication	Year of Pediatric Approval	Route and Frequency of Admin.	Efficacy Information	Important Safety and Tolerability Issues
Oxcarbazepine (OXC)	• Monotherapy in the treatment of partial seizures in children 4-16 years Adjunctive therapy in the treatment of partial seizures in children 2-16 years	2000 (adjunctive use in pediatric POS)	PO, BID Weight-based dosing ages 2-16	Monotherapy – 4 RPCTs demonstrated efficacy in patients ages 8 and older primarily using study exit due to seizure as the efficacy measure. A 5th study in patients 1 mo to 16 years did not demonstrate efficacy, but this failure was felt to be due to design flaws, not lack of efficacy Adjunctive POS: 3 efficacy trials incl. pediatric patients (15 to 66 yrs, 3-17 yrs, and 1 mo to 4 yrs). Primary efficacy endpoint was between-group comparison of the percentage change in partial seizure frequency in the double-blind treatment phase relative to baseline phase for the 2 RCPTs, both of which favored OXC over placebo. For the 3rd pediatric trial (1 mo to 4 yrs) the 1° endpoint was change in seizure frequency per 24 hours compared to the seizure frequency at baseline, which also statistically favored OXC, but no evidence of effectiveness below age 2 yrs.	Hyponatremia, Anaphylactic Reactions and Angioedema, SJS and TEN (both seen in children and adults), DRESS, hematologic abnormalities, risk of seizure aggravation (especially PGTC) Cognitive/Neuropsychiatric Adverse Reactions (cognitive slowing, somnolence, coordination abnormalities) seen in pediatric patients,

Product (s) Name	Relevant Pediatric Indication	Year of Pediatric Approval	Route and Frequency of Admin.	Efficacy Information	Important Safety and Tolerability Issues
Pregabalin (PGB)	Treatment of partial-onset seizures in patients 1 month of age and older	2018 (down to age 4) 2019 (down to 1 month)	PO only Weight-based dosing	1 mo to 4 years: Primary efficacy endpoint of change from baseline in log-transformed 24 hour seizure frequency as determined by 48-72 hour video-EEG read by a central reader.	Warnings and Precautions: Angioedema, hypersensitivity reactions, increased seizure frequency if withdrawn rapidly, risk of suicidal thoughts and behaviors, peripheral edema, dizziness, somnolence and potential to impair ability to drive
Tiagabine (TGB)	Adjunctive therapy in adults and children 12 years and older in the treatment of partial seizures		PO, BID	3 RPCTs with primary endpoint of median reduction in seizure frequency in patients with POS (statistically favored TGB over placebo)	Cognitive/Neuropsychiatric Adverse Events (impaired concentration and somnolence), Generalized Weakness, serious rash

Product (s) Name	Relevant Pediatric Indication	Year of Pediatric Approval	Route and Frequency of Admin.	Efficacy Information	Important Safety and Tolerability Issues
Topiramate (TPM)	• Initial monotherapy in patients ≥2 years of age with POS or PGTCS Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with POS or PGTCS	2009 (pediatric adjunctive POS)	PO, BID Weight-based dosing ages 2-9 yrs	Monotherapy: RCT (high dose [400 mg] vs low dose [50 mg] TPM) in pts ≥10 yrs with POS or PGTCS. Primary endpoint was between-group comparison of time to first seizure during the double-blind phase, which statistically favored the high dose. Monotherapy in pts 2-9 yrs was demonstrated via PK bridging. Adjunctive: 1 RPCT in POS patients 2-16 yrs and 1 RCPT in patients ≥2 yrs with PGTCS. Primary efficacy endpoint was median percent reductions in seizure rates compared to baseline, vs placebo. Both studies had statistically significant reduction in MSF.	Warnings for adult and pediatric patients: Acute Myopia and Secondary Angle Closure Glaucoma, Visual Field Defects, Oligohidrosis and Hyperthermia, Metabolic Acidosis, Cognitive/ Neuropsychiatric Adverse Reactions (lower in peds than adults), Hyperammonemia and Encephalopathy, Kidney Stones,
Valproate, Valproic Acid (VPA)	Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures, ages 10 yrs and older		PO/IV, TID or BID depending on formulation	2 RPCTs in patients (patient ages not identified), primary endpoint was reduction in seizures compared to baseline vs placebo, with statistically significant difference.	Hepatotoxicity (including fatalities) particularly in patients < 2 yrs and in first 6 mos of treatment. Other warnings: Birth defects, Pancreatitis, thrombocytopenia, hyperammonemia, hypothermia, somnolence

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

LCM was approved in the United States on October 28, 2008 as adjunctive therapy for the treatment of POS in patients greater than or equal to 17 years of age in oral tablets and solution for intravenous (IV) infusion. Oral solution was added in 2010 and it was approved for monotherapy and with an initial starting loading dose in 2014. As noted above, the indication was extended to pediatric patients 4 years and older for the oral formulations only in 2017. Most recently, in November 2020, LCM was approved for the adjunctive treatment of PGTCS in patients 4 years and older. The intravenous formulation was also extended for use in patients down to 4 years of age as temporary replacement when oral LCM is not feasible.

The present supplement aims to fulfill Pediatric Research Equity Act (PREA) Post-Marketing requirements: PMR 3288-1, 2774-1, and 3293-1 for patients 1 month to less than 4 years of age. See Section 11 for a list of remaining outstanding PREA PMRs.

Table 2 PREA PMRs for NDA 022253, 022254, 022255 Addressed by this Supplement

PMR 3288-1 (NDA 22253, 22255, oral tablet and oral solution)	A prospective, randomized, controlled, double-blind, efficacy, PK, and safety study of the adjunctive use of LCM for the treatment of POS 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 PK analysis must also be performed to determine a dosing regimen for the monotherapy use of LCM in pediatric patients ages 1 month to <4 years of age. Study Completion: Sep 2020 Final Report Submission: Mar 2021	SP0967, EP0034, SP848, and CL0447 Part IV (Population PK study report) will fully address the postmarketing requirement
PMR 3293-1 (NDA 022254 injection)	Deferred pediatric studies under PREA for the treatment of POS in pediatric patients ages 1 month to <4 years. Study Completion: Mar 2021 Final Report Submission: Sep 2021	EP0060 will fully address the postmarketing requirement
PMR 2774-1 (NDA 022254 injection)	A safety study of replacement of oral dosing with iv dosing administered over 30 to 60 minutes in pediatric patients 1 month to <17 years of age with POS. If safety is acceptable, a replacement study at a faster rate of infusion (15 minutes) must be conducted in this population. Sparse PK samples must be collected to evaluate the	EP0060 will fully address the postmarketing requirement to cover the ≥ 1 month to < 4 years of age

	PK of LCM and its metabolite using PPK approach in this population. Final Report Submission: Sep 2021	

Reviewer-verified from Module 1.17.2, PMR PREA correspondence, Table 1.1

3.2. Summary of Presubmission/Submission Regulatory Activity

The original protocol for Study SP0967 was the subject of Special Protocol Assessment agreed upon on January 7, 2015. The Applicant had several interactions with the Division regarding the difficulties with the recruitment and conduct of Study SP0967, including a Type C WRO meeting in January 2018, with a follow-up clarification teleconference in Feb 2018, and a subsequent SPA amendment in April 2018. At that Type C meeting, the Applicant detailed the many challenges with the conduct of SP0967, including inconsistencies with video-EEG interpretation between the local reader (for study eligibility) and the central reader (for endpoint analysis). The Applicant felt the study was unfeasible, but the Division encouraged the Applicant to continue the study without the central reader (as implemented in the SPA Amendment (Protocol Amendment 3)).

The Applicant then submitted a meeting request in September 2020 to discuss the path forward for this supplemental application, given the negative study results from Study SP0967, and also in the context of the FDA Guidance on Extrapolation of Efficacy from Adults to Pediatric Patients 2 years of Age and Older. The Division indicated in the Written Responses on November 30, 2020 that it had recently determined that it is acceptable to extrapolate to pediatric patients 1 month of age and older the effectiveness of drugs approved for the treatment of POS in adults and supported the Applicant's plan to submit a supplemental NDA including the use of pediatric extrapolation to support a claim of efficacy in the pediatric population of patients greater than or equal to 1 month to less than 4 years of age.

3.3. Foreign Regulatory Actions and Marketing History

LCM is approved in more than 70 countries. In the EU, LCM has been approved as monotherapy and adjunctive therapy in the treatment of POS in patients 4 years and older in all formulations (oral tablet, oral solution, and iv infusion).

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI inspections were waived for this supplement review.

4.2. Product Quality

Vimpat is an already approved product. As part of this NDA supplement, the Applicant proposes an increase of the in-use shelf life for LCM oral solution from 7 weeks to 6 months. The reason given for this change is to allow the proposed younger patients (1 month to less than 4 years of age) additional time to consume the full contents of the bottle container, because these patients will be prescribed a smaller volume of LCM 10 mg/mL oral solution per day compared to older pediatric patients and adults. The Applicant conducted a 180-day in-use stability study to support this proposed change.

Please see the Office of Pharmaceutical Quality (OPQ) review by Dr. Richard T. Matsuoka and Dr. Gurpreet Gill-Sangha for full details. The OPQ team concludes that the proposed increase of the in-use shelf-life for the LCM oral solution from 7 weeks to 6 months is acceptable.

4.3. Clinical Microbiology

No new clinical microbiology studies were included in this NDA supplement.

4.4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were included in this NDA supplement.

4.5. Clinical Pharmacology

Efficacy in pediatric patients with POS from 1 month to less than 4 years of age is based on extrapolation of dose-exposures in the adult population to that of the pediatric population.

Please see the Office of Clinical Pharmacology review by Dr. Adarsh Ghandi for a full discussion of the pharmacokinetics and the methods used to support effectiveness through extrapolation.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

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Table 3 Listing of Clinical Trials Relevant to this NDA Supplement

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Studies to Support Safety						
SP0967	NCT 02477839	Phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to investigate the efficacy and safety of LCM as adjunctive therapy in study participants with epilepsy ≥ 1 month to < 4 years of age with POS	Oral, 4-12 mg/kg/day	Change in Average Daily Frequency (ADF) of Electrographic Partial-Onset Seizures from End-of-Baseline Period video-EEG to End-of-Maintenance Period Video EEG	7-day baseline period, double-blind treatment for a 20-day Titration Period and a 7-day Maintenance Period, followed by a 12-day Transition Period if patients enter OLE or 16-day Taper Period	255 patients	Patients > 1 month to < 4 years of age with epilepsy and POS. Patients had to have at least 2 partial-onset seizures in 24 hours on baseline video-EEG to be enrolled in the study	25 Countries
EP0060	NCT 02710890	Phase 2/3, multicenter, open-label study to evaluate the safety and tolerability of intravenous LCM in pediatric subjects ≥ 1 month to < 17 years of age with epilepsy	IV, single-dose *potential for Q12 dosing up to 10 doses Dose range: 2-12 mg/kg/day or 100 -600 mg/day	Safety	Minimum 1 day, up to 5 days with a final visit following the last dose and telephone visit 1-3 days after Final Visit	103 patients	Patients 1 month to < 17 years of age with epilepsy and: Open-label LCM (OLL): patients currently receiving oral LCM in an open-label long-term study Prescribed LCM (RxL): patients	22 sites in 5 countries (US, Ukraine, Poland, Hungary, Italy)

							currently receiving prescribed oral LCM from commercial supply Initiating iv LCM (IIL): patients not currently receiving LCM and receiving first dose in the study	
SP0847	NCT 00938431	Phase 2, multicenter, open-label study to investigate the safety, tolerability, and pharmacokinetics of LCM oral solution (syrup)	8-12 mg/kg/day	Primary outcome measure – safety Secondary Outcome was change in seizure frequency from baseline to end of treatment period	13 weeks	47 patients	1 month to 17 years of age with uncontrolled POS when added to 1-3 other antiepileptic drugs	Belgium, Mexico, United States
SP0848	NCT 00938912	Phase 2, multicenter, long-term, open-label extension study	2-12 mg/kg/day, (maximum 600 mg/day) with dose titration	Safety	Up to 2 years	366 patients	Patients 1 month to ≤ 17 years of age with partial-onset seizures	Eight countries (Belgium, France, Germany, Hungary, Japan, Mexico, Poland, United States
EP0034	NCT 01964569	Phase 3, multi-center, open-label, long-term extension study of safety and efficacy	2-12 mg/kg/day, oral tablet, or oral	Safety	Up to 2 years	540 patients	Pediatric patients age 1 month to < 17 years of age with	35 countries

			solution				partial onset seizures, previously enrolled in SP0967 or SP0969	

Source: Reviewer adapted Table from clinicaltrials.gov and Section 2.7.6 Synopses of Individual Studies
LCM = lacosamide, OLE = open-label extension

5.2. Review Strategy

This clinical review will primarily examine the safety from Study SP0967, a Phase 3 safety and efficacy study of the use of LCM for the treatment of POS in pediatric patients 1 month to less than 4 years of age. I will also examine the safety from the open-label safety studies, EP0034 and SP0848 and the safety from the open-label safety study, Study EP0060,of the use of intravenous LCM in this patient population. I will also include a review of the postmarketing database in this patient population, as it has been used off-label in pediatric patients since LCM was initially approved in 2008.

All of the data will be reviewed independently, and I will perform my own safety analyses based on the submitted safety data provided by the Applicant. Safety analyses will focus on safety in patients less than 4 years of age, as LCM is already approved in both oral and intravenous formulations in patients greater than 4 years of age and data on patients greater than 4 years of age have already been reviewed.

Efficacy will be established through extrapolation as noted above.

6. Review of Relevant Individual Trials Used to Support Efficacy

No independent efficacy studies were reviewed for this supplement. As noted above, the Division determined that it is acceptable to extrapolate to pediatric patients 1 month and older the effectiveness of drugs approved for the treatment of POS in adults. Efficacy is therefore established through extrapolation from adult clinical trials, as described in labeling, as well as through clinical pharmacology population PK simulation and modeling studies as described in the Office of Clinical Pharmacology review.

<u>Failed Study SP0967</u>
SP0967 is outlined above in Table 3. It was a double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of LCM 8 mg/kg/day to 12 mg/kg/day as adjunctive therapy in patients with epilepsy greater than or equal to 1 month to less than 4 years of age with uncontrolled POS. As noted above, SP0967 was the subject of a Special Protocol Assessment (SPA) agreement. The study design is briefly described here.

The efficacy variables were based on video-EEGs (at least 48 hours of continuous interpretable recording). Partial-onset seizure count was based on electrographic seizures which were to be recognizable ictal patterns on at least 2 contiguous electrodes, initiated as a unilateral or strongly asymmetric abnormal epileptiform discharge, lasting a total of greater than 10

seconds. The study comprised of a 7-day Baseline Period, a 20-day blinded Titration Period to attain the target dose, a 7-day Maintenance Period (no dose adjustments allowed during this period), and a 12-day blinded Transition Period for patients who completed the study and chose to enter the open-label extension study (EP0034) or a Taper Period, followed by a 30-day Safety Follow-up Period for patients who chose not to enter EP0034.

Randomization occurred after completion of the End-of-Baseline video-EEG and confirmation that patients had met the selection criteria, and it was stratified by age category (greater than or equal to 1 month to less than 6 months, greater than or equal to 6 months to less than 1 year, greater than or equal to 1 year to less than 2 years, and greater than or equal to 2 years to less than 4 years of age). Patients were randomized 1:1 to study drug or placebo.

The primary efficacy variable in the United States was the change in average daily frequency (ADF) of electrographic POS as measured on the End-of-Maintenance Period video-EEG compared to the End-of-Baseline Period video-EEG. The secondary efficacy variables were the percent and absolute change in ADF of electrographic POS from the End-of-Baseline Period video-EEG to the End-of-Maintenance Period video-EEG, the proportion of patients who achieved "seizure-free" status from all seizures types and from POS types only during the End-of-Maintenance Period video-EEG, and proportion of patients experiencing a greater than or equal to 25% to less than 50%, 50% to 75%, or greater than 75% reduction in ADF of electrographic POS from the End-of-Baseline Period video-EEG to the End-of-Maintenance Period video-EEG, among a few others. The partial-onset seizure count was based on electrographic seizures only for patients greater than or equal to 1 month to less than 6 months of age (with or without clinical correlate) and partial-onset seizure count for children greater than 6 months to less than 4 years of age was based on electrographic seizures with an accompanying clinical correlate.

The study failed to reach statistical significance on the primary endpoint, with a percent reduction for LCM over placebo in ADF of 3.19% (95% CI: -13.59, 17.50, p = 0.6895). All sensitivity analyses of the primary efficacy variable for the US supported the conclusions of the primary analysis.

Reviewer's comment: Study SP0967 failed to demonstrate superior efficacy of LCM as compared with placebo in patients greater than or equal to 1 month to less than 4 years of age with uncontrolled POS. However, there were many challenges to the conduct and interpretation of the efficacy results for Study SP0967 that likely resulted in the study failure and inability to reach statistical significance on the primary or secondary endpoints.

While placebo-controlled studies are considered essential for determination of effectiveness in studies for the treatment of POS, especially given high interpatient variability in severity, frequency, and duration of seizures, there is also significant difficulty with recruitment in this

age range, especially with the overly burdensome requirement for 48-72 hours of inpatient video-EEG to be completed twice, only 3 weeks apart. The Applicant struggled to recruit sites and patients for this study which was initiated in 2015 and completed in 2020.

At the time of study design, it was felt that video-EEG was the most accurate measure of seizure frequency in the youngest patients, given the equally high likelihood of finding electrographic seizures without clinical correlate, or non-epileptic movements that may be mistaken as seizures by a caregiver. Therefore, the video-EEG requirement for assessment both at baseline and at the end of the maintenance period, to be read by a blinded central reader, was considered the most reliable and accurate method of determining the primary endpoint. However, the video-EEG requirement is labor- and resource-intensive and was also a source of the recruitment challenges.

Finally, this reviewer notes that the patient population available for such a study has changed with time, the increased capacity of neuroimaging to detect structural lesions earlier in patients with focal epilepsy leading to more frequent surgical resection in the youngest patients, as well as newer AEDs available for off-label use that make enrollment in a placebo-controlled study less desirable for both patients and physicians. These changes have resulted in a more challenging, more refractory, and sometimes more ill-defined population of patients with POS who were eligible for the study. The Applicant documented significant challenges with the reading of the video-EEGs, with high inter-rater variability and low inter-rater reliability of the interpretation of the seizure types and seizure counts of the primary endpoint measure. Many of the patients who were initially confirmed as eligible for the study by the local EEG reader (greater than 2 daily electrographic partial-onset seizures on video-EEG) were subsequently determined to be ineligible for the study because the central reader did not agree that the EEG showed the required 2 electrographic partial-onset seizures. After multiple attempts to improve the inter-reader reliability, the Applicant planned to stop the study at this point given the technical challenges with the EEG interpretation and what appeared to be a lack of feasibility. The Division encouraged the Applicant to continue to collect the data, since the study was ongoing, and to instead rely on the local readers to read the End-of-Baseline and End-of-Maintenance Video EEGs for the analysis of the primary endpoint, and to eliminate the central reader.

Given these challenges in the study design and execution, the failure of the study to meet statistical significance does not indicate a lack of effectiveness of LCM in the treatment of POS in this population. Therefore, extrapolation of efficacy from the adult patient to the pediatric patient down to age 1 month is appropriate.

7. Integrated Review of Effectiveness

As noted above, efficacy was established through pediatric extrapolation. No independent efficacy analyses were reviewed.

8. Review of Safety

8.1. Safety Review Approach

Safety was reviewed from Study SP0967 for the safety of LCM in patients 1 month and older (oral formulations). Safety was also reviewed from Study EP0060 for the safety of patients 1 month to less than 4 years of age for the intravenous formulation. These data were previously reviewed as part of the approval of the intravenous formulation in older pediatric patients 4 years to less than 17 years (sNDA 022254- S-38). The data from open-label extension studies EP0034 and SP0848 were also reviewed for any unique or serious adverse events.

This review will focus primarily on patients 1 month to less than 4 years of age, because the data in older pediatric patients have already been reviewed for other prior efficacy supplements.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

There were 255 total patients treated in Study SP067. Table 4 below summarizes median duration and total daily dose in the treatment and maintenance period.

Table 4 Exposure to Study Medication in SP0967

	LCM N = 128	Placebo N = 127
Treatment Period	N = 128	N = 127
Study medication duration (days)		
N	128	127
Mean (SD)	27.7 (3.8)	27.4 (2.6)
Median (min, max)	27.0 (3, 44)	27.0 (6, 32)
Median total daily dose (mg/kg/day)		
N	128	127
Mean (SD)	9.1 (1.6)	9.2 (1.4)
Median (min, max)	10.0 (3, 12)	10.0 (3, 11)
Maintenance Period	N = 128	N = 127
Study medication duration (days)		
N	124	125
Mean (SD)	7.6 (2.5)	7.2 (1.7)
Median (min, max)	7.0 (3, 21)	7.0 (3, 12)
Median total daily dose (mg/kg/day)		

N	123	125
Mean (SD)	10.8 (1.5)	10.9 (1.4)
Median (min, max)	12.0 (4, 13)	12.0 (8, 12)

Source: Reviewer-adapted from SP0967 CSR Table 10.1.1

The long-term extension studies also characterized exposure of the patients in this age population (See Table 5).

Study SP848 enrolled 324 patients, including 37 patients greater than or equal to 1 month to less than 4 years of age. Ten of these patients have completed the study, with a mean modal daily dose of 9.0 mg/kg/day.

Study EP0034 is an ongoing study of 517 patients, 195 of whom are patients greater than or equal to 1 month to less than 4 years of age. The patients all participated in a double-blind, placebo-controlled study prior to enrolling in the open-label extension. Of the 195 patients in this age group, 100 of them (51.3%) have been exposed for > 12 months, and 52 patients (26.7%) have been exposed for greater than o24 months (study ongoing). The mean modal daily dose in this age group is 10.0 mg/kg/day.

Table 5 Study SP848 and EP0034 Summary of LCM Overall Exposure (greater than or equal to 1 month to less than 4 years)

LCM exposure	Study SP848 N = 37 n (%)	Study EP0034 N = 195 n (%)
>0 months	37 (100)	195 (100)
>6 months	37 (100)	140 (72)
>12 months	31 (84)	100 (51)
>18 months	11 (30)	73 (37)
>24 months	8 (22)	52 (27)

LCM = lacosamide, Reviewer-adapted from SCS Table 1-5 and Table 1-7

In EP0060, there were 26 patients in the greater than or equal to 1 month to less than 4 years of age group. All of these patients received either 1 or 2 doses of intravenous LCM in the study.

The disposition of the patients in the double-blind study SP0967 are presented in Table 6 below.

Table 6 SP0967 Patient Disposition and Discontinuation Reason (Safety Set)

Disposition	LCM N = 128 n (%)	Placebo N = 127 n (%)	Total N = 255 n (%)
Randomized	128 (100)	127 (100)	255 (100)
Completed Study	118 (92)	124 (98)	242 (95)
Early Discontinuation	10 (8)	3 (2)	13 (5)

Adverse Event	1 (1)	0	1 (0.5)
Lack of Efficacy	0	0	0
Protocol Violation	2 (2)	0	2 (1)
Lost to follow-up	0	0	0
Consent withdrawn	3 (2)	3 (2)	6 (2)
Other	4 (3)	0	4 (2)

LCM = lacosamide, Reviewer-adapted and verified from SP0967 CSR and SCS Table 1-14

8.2.2. Relevant characteristics of the safety population:

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Table 7 Demographics and Baseline Characteristics of Safety Population SP0967

Demographic Parameters	LCM N = 128 n (%)	Placebo N = 127 n (%)	Total LCM N = 255 n (%)
Sex			
Male	71 (55)	75 (59)	146 (57)
Female	57 (45)	52 (41)	109 (43)
Age (years)			
Mean (SD)	2.1 (1.1)	2.2 (1.1)	2.2 (1.1)
Median	2.1	2.2	2.2
Min, Max	0.11, 3.9	0.25, 3.9	0.11, 3.9
Age Group			
≥ 1 mo to < 6 months	8 (6)	6 (5)	14 (5)
≥ 6 months to < 1 year	18 (14)	16 (13)	34 (13)
≥ 1 to < 2 years	36 (28)	37 (29)	73 (29)
≥ 2 to < 4 years	66 (52)	68 (53)	134 (53)
Weight (kg)			
Mean (SD)	11.3 (3.8)	11.7 (3.4)	11.5 (3.6)
Median	11	12	11.2
Min, Max	4, 22.8	4.1, 21.6	4, 22.8
Race			
White	94 (73)	101 (79)	195 (77)
Black or African American	2 (2)	0	2 (1)
American Indian	13 (10)	5 (4)	18 (7)
Asian	14 (11)	15 (12)	29 (11)
Other/Mixed	5 (4)	6 (5)	11 (4)
Ethnicity			
Hispanic or Latino	26 (20)	20 (16)	46 (18)
Not Hispanic or Latino	102 (80)	107 (84)	209 (82)
Region			
United States	7 (5)	5 (4)	12 (5)
Eastern Europe	76 (60)	86 (68)	162 (63)
Western Europe*	7 (5)	5 (4)	12 (5)
Asia/Pacific/Other	16 (13)	17 (13)	33 (13)
Mexico/South America	22 (17)	14 (11)	36 (14)

Source: Reviewer-derived from SP0967 ADSL dataset
LCM = lacosamide; SD = standard deviation
**Western Europe includes France, Italy, and Portugal*

Table 8 Demographics of Safety Population EP0060 1 month to less than 4 years of age

Demographic Parameters	LCM ≥ 1 mos to < 4 years N = 26 n (%)
Sex	
Male	12 (46)
Female	14 (54)
Age (years)	
Mean (SD)	2.1 (1.4)
Median	2.4
Min, Max	0.17, 3.9
Age Group	
≥ 1 mo to < 6 months	26 (100)
≥ 6 months to < 1 year	0
≥ 1 to < 2 years	0
≥ 2 to < 4 years	0
Weight (kg)	
Mean (SD)	11.1 (4.3)
Median	12.1
Min, Max	4.8, 18.5
Race	
White	26 (100)
Black or African American	0
American Indian	
Asian	0
Not specified	
Ethnicity	
Hispanic or Latino	1 (4)
Not Hispanic or Latino	25 (96)
Region*	
North America	0
Europe	26 (100)
Asia/Pacific/Other	
Latin America	
Enrollment Type	
IIL	24 (92)
OLL	0
RxL	2 (8)
Assigned Infusion Duration	
15-30 minutes	5 (19)
30-60 minutes	21 (81)
Total Number Infusions	
1 infusion	13 (50)
2 infusions	13 (50)
>2 infusions**	0

Source: Reviewer derived from EP0060 ADSL dataset

8.2.3. Adequacy of the safety database:

Given that LCM has already been approved in the United States since 2008 with extensive experience with the oral and intravenous formulations in adults, as well as the safety of oral

LCM in pediatric patients, the total safety database of 258 patients between 1 month to less than 4 years of age, with 131 of them receiving treatment for greater than 12 months, is adequate.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There were no concerns regarding the integrity of the data submitted for the safety review. The datasets provided by the Applicant were complete and I was able to reproduce sufficiently the safety analyses of the Applicant and to perform my own analyses when necessary.

8.3.2. Categorization of Adverse Events

For Study SP0967 and Study EP0060, MedDRA version 16.1 was used to code adverse events.

An Adverse Event (AE) was defined as any untoward medical occurrence in a patient administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medical product (IMP), whether or not related to the IMP.
Serious Adverse Event (SAE) were defined per the usual criteria:

- Death
- Life-threatening
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect
- Important medical e vent that based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the other outcomes listed in this definition
- Initial inpatient hospitalization or prolongation of hospitalization

AEs of special interest included any AE that a regulatory authority mandated reporting on an expedited basis, regardless of the seriousness, expectedness, or relatedness and included:

- The following arrhythmias: atrial fibrillation/flutter, ventricular tachycardia or fibrillation, AV block, and marked bradycardia (< 45 bpm).
- Syncope of loss of consciousness (other than seizure-related)
- Serious suspected multiorgan hypersensitivity reactions
- Potential Hy's Law, as defined in the protocol

For the safety analysis, a few of the AEs were recoded to avoid splitting. The following AEs were recoded:

Table 9 Recoded AE Terms for Reviewer Analysis (SP0967)

Old Terms	Recoded Term
Eosinophil count increased, eosinophilia	Eosinophilia
Alanine aminotransferase increased, liver function test abnormal	Liver function test abnormal
Mood swings, mood altered	Mood altered
Convulsion, epilepsy, partial seizures	Convulsion
Body temperature increased, hyperthermia, pyrexia	Pyrexia

8.4. Safety Results

8.4.1. Deaths

There were no deaths during study SP0967, except in one patient who was ineligible to participate and was not randomized to treatment. There were no deaths in the intravenous safety study, EP0060.

In the open-label extension studies, there were 4 deaths in patients 1 month to less than 4 years of age. The narratives for the deaths are outlined below.

Sp0967-(b) (6), *Respiratory Failure*

1.5 year-old male (weight 7.9 kg), with a complex medical history including lissencephaly, multiple congenital anomalies, optic atrophy, respiratory tract malformation, atrial septal defect, and severe developmental delay on concomitant phenobarbital, levetiracetam, and topiramate, with the addition of clonazepam and diazepam at the time of the respiratory failure. Patient initially enrolled in SP0967 and received first dose of placebo on (b) (6). He completed the study (b) (6) and enrolled in EP0034. Initially had nonserious adverse events of upper respiratory tract infection and cough in (b) (6) He had had an SAE of respiratory distress associated with respiratory infection on (b) (6) at which times he was on LCM 10 mg/kg/day. Six months later on (b) (6) he developed another SAE of liver function test abnormal, moderate in intensity identified on routine laboratory tests. Had recently decreased dose to 5 mg/kg/day x 1 day. On the same day he had decreased platelet count, nonserious AE of ECG T wave inversion and drug was withdrawn due to the elevated AST (253), ALT(166) and low platelet counts. GGT was also elevated at 273 with normal total bilirubin. Patient was asymptomatic and the event resolved. On (b) (6), he was hospitalized for respiratory distress, periorbital cellulitis of a prosthetic eye, and placed on positive airway pressure from which he recovered. He then experienced a fatal event of respiratory failure on (b) (6) at which time he was not taking any study drug x 62 days.

SP0967-(b) (6) *Aspiration pneumonia*

1.3 year-old male (weight 8.0 kg) with a history of cerebral palsy, malnutrition, salivary hypersecretion, and aspiration pneumonia on concomitant clobazam, valproate, and carbamazepine and domperidone. Patient participated in SP0967 and received placebo with the first dose on (b) (6), and completed the study on (b) (6) and entered EP0034. He experienced an SAE of sepsis on (b) (6) 19 days after study drug initiation (on 12 mg/kg/day). He remained hospitalized then experienced an SAE of aspiration pneumonia on (b) (6) 28 days after study drug initiation (12 mg/kg/day x 11 days). Drug was withdrawn with final dose on (b) (6). On (b) (6) he experienced severe bradycardia, apnea, and respiratory failure and became comatose. He died in the hospital on the same day, with a cause of death of blood infection, aspiration pneumonia, and worsening epilepsy due to fever.

SP0967-(b) (6), *Respiratory failure*

0.7-year-old (weight 7.6 kg) on concomitant levetiracetam and valproate. Received placebo in Study SP0967, starting on (b) (6), and completing study on (b) (6). He enrolled in EP0034, and initiated LCM at 5 mg/kg/day. He had an SAE of respiratory failure on (b) (6) 420 days after drug initiation. At the time he was on 10 mg/kg/day. His mother heard crying and screaming while the child was sleeping, and he was found pale, with cold sweat, and breathing heavily. He was admitted to the hospital with reduced breathing, and he died later that day.

SP0967-(b) (6) Pneumonia, probably H1N1 virus

4-year-old (weight 17.0 kg) with a history of epilepsy, psychomotor retardation, and tonsillitis, who was on concomitant lamotrigine, topiramate, valproic acid, and montelukast. He was enrolled in SP0967 with first dose (b) (6), completed the study, and enrolled in EP0034 on (b) (6) He had an SAE of pharyngotonsillitis requiring hospitalization and antibiotics on (b) (6) and a nonserious AE of bacterial rhinitis on (b) (6) He subsequently developed an SAE of pneumonia/influenza on (b) (6) 701 days after study drug initiation. He was taking 4 mg/kg/day of LCM at this time, and it was recently decreased from 6 mg/kg/day. He presented with fever and oxygen saturation of 30% and diagnosed with pneumonia requiring intubation. He was diagnosed with H1N1 influenza pneumonia and died on (b) (6)

Reviewer's comment: The 4 deaths detailed above in the open-label extension studies do not appear related to treatment with LCM. There are no new safety signals identified upon review of these deaths in the patient population 1 month to less than 4 years of age.

8.4.2. Serious Adverse Events

In Study SP0967, there were 4 patients in each treatment arm that developed SAEs as outlined in the table below.

Table 10 SP0967 Serious Adverse Events (SAEs)

SOC and PT	LCM N = 128 n(%)	Placebo N = 127 n(%)
Any SAE	4 (3)	4 (3)
Gastrointestinal disorders	2 (2)	0
Vomiting	2 (2)	0
Nervous system disorders	2 (2)	0
Convulsion	2 (2)	0
Infections and infestations	0	2 (2)
Upper respiratory tract infection	0	1 (1)
Urinary tract infection	0	1 (1)
General Disorders and Administration Site	0	1 (1)
Pyrexia	0	1(1)
Injury, poisoning and procedural complications	0	1 (1)
Thermal burn	0	1 (1)
Respiratory, thoracic, and mediastinal disorders	0	1 (1)
Respiratory Failure	0	1 (1)

Source: Reviewer Adapted from Study 0967 CSR Table 11.3.1
LCM = lacosamide, SOC = system organ class, PT = preferred term, SAE = serious adverse event

The narratives for the SAEs for the patients receiving LCM are described below. There were additional SAEs that occurred during the Transition Period after initiation of LCM, in patients who initially received placebo in the double-blind treatment period, and these narratives are also included below. There were the 4 SAEs detailed above, and another 4 in the Transition Period (1 each for pneumonia, aspiration pneumonia, herpes/dehydration, and viral infection).

(b) (6) *convulsion*

3.17-year-old male (weight 15 kg), with complex medical history including h/o neonatal asphyxia and acute renal failure with epilepsy. Concomitant medications were carbamazepine, metoprolol, minoxidil, and ramipril. He was randomized to LCM and received first dose 4 mg/kg/day on (b) (6) He experienced first SAE of convulsion requiring hospitalization 10 days later, on (b) (6) during the Titration period. He was on 8 mg/kg/day (x 1 day) at the time of event. He received diazepam and had no further seizures. Dose was unchanged. He experienced a second SAE of convulsion requiring hospitalization on (b) (6) during the Transition Period, 31 days after drug initiation. It was moderate, he was receiving 12 mg/kg/day and he received diazepam. Dose was not change and patient resolved and completed study.

(b) (6), *vomiting*

2.97-year-old female (weight 12.0 kg), with a medical history of hydronephrosis, epilepsy, and speech disorder on concomitant carbamazepine, enrolled in SP0967, received initial dose of LCM 4 mg/kg/day on (b) (6). She initially experienced decreased appetite (non-serious event) on (b) (6) which was moderate and felt to be related. One week later, on (b) (6) the patient vomited 12 times and went to the ER where she received intravenous fluid and also experienced neutropenia. Dose was not changed, vomiting resolved. Patient continued in the study until (b) (6) when parents decided to stop giving the patient the medication.

(b) (6), *vomiting*

2.17-year-old male(weight 10.5 kg), with past medical history of encephalopathy, hemiplegia, s/p multilobar resection of occipital and parietal lobe, with dysphagia and refractory epilepsy, on concomitant carbamazepine, clobazam, and levetiracetam. He enrolled in study, initiated LCM on (b) (6). He experienced an SAE of vomiting during the Titration Period, on (b) (6) 13 days after drug initiation. Vomiting was moderate in intensity, felt to be related to drug, and required hospitalization and treatment with ondansetron and electrolytes. Dose was unchanged, patient completed the study and patient entered open-label extension study EP0034.

(b) (6), *convulsion*

3.42-year-old male (weight 11.4 kg), with a complex medical history including Pierre-Robin syndrome, congenital hydrocephalus, Dandy-Walker syndrome, and epilepsy, on concomitant levetiracetam, in addition to hydrocortisone, lansoprazole, and levothyroxine. Patient enrolled in study, received first dose of LCM (b) (6) and experienced an SAE of convulsion due to recurrent seizures on (b) (6) 15 days after drug initiation during the Titration Period. The seizures were mild, but the second seizure required rectal diazepam treatment. The dose was not changed. Patient had another nonserious adverse event of convulsions requiring diazepam on (b) (6) Patient completed study. Dose was not changed. Pt entered open-label extension EP0034.

Pt (b) (6), *herpes gingivostomatitis, dehydration (Transition Period)*

1.92 year-old female patient (weight 12 kg) with history of epilepsy and brain neoplasm s/p surgical resection on concomitant clonazepam, lamotrigine and valproic acid. She received placebo and completed the double-blind treatment period and entered the Transition Period. She was receiving LCM for 5 days in the Transition Period when she experienced a second adverse event of oral herpes with associated dehydration leading to hospitalization. She had

previously experienced a non-serious AE of oral herpes prior to initiation of LCM. The event did not result in change of the LCM dose and the patient completed the study and entered the open-label extension.

(b) (6), *aspiration pneumonia (Transition Period)*
1.1-year-old male (weight 8 kg), with a history of malnutrition, cerebral palsy, salivary hypersecretion, and aspiration pneumonia who has 8 seizures a day at baseline. He was on concomitant carbamazepine, clobazam, and valproate for seizures. He was randomized to placebo and received first dose on (b) (6). (b) (6) he entered the Transition Period, and 5 days later, on (b) (6) he experienced a serious adverse event of pneumonia aspiration requiring hospitalization. He continued in the study, dose was not changed, the pneumonia resolved, and he entered the open-label extension study.

(b) (6) *viral infection (Transition Period)*
1.83-year-old male (weight 12.7 kg), with a history of asphyxia, congenital heart disease, stroke, and infantile spasms with refractory epilepsy on concomitant lamotrigine, topiramate, hydrocortisone, and levothyroxine. Initiated LCM on (b) (6) and experienced an SAE of viral infection 34 days later on (b) (6) during the Transition Period. He developed fever, vomiting and somnolence related to the viral infection, requiring hospitalization and rehydration. The dose was not changed, and patient completed study and entered OLE, EP0034.

(b) (6), *pneumonia, (Transition Period)*
2.80-year-old male (weight 10.0 kg), with medical history of quadriparesis, epilepsy, with average 6.4 seizures per day, and on concomitant clonazepam and valproic acid. Initiated treatment in the study on (b) (6) and experienced an SAE of pneumonia on (b) (6) during the Transition Period, 39 days after drug initiation. The event was moderate, reported to be not related to drug, and patient had been at a stable dose for 27 days. He required hospitalization and treatment with ceftriaxone, and it resolved on (b) (6) Dose was unchanged, patient completed study, and entered open-label extension EP0034.

Reviewer's comment: Although it is difficult to discern if the SAEs of convulsion are related to treatment or the patient's underlying epilepsy, both patients with an SAE of convulsion continued on treatment in the study without a change to the dose and continued into the open-label extension. Although there were no placebo patients who experienced an SAE of convulsion, it does not appear to be a safety signal given that the patients did not discontinue from these events. There appears to be a potential signal for vomiting in the above cases, given 2 serious events of vomiting requiring rehydration. Vomiting is already listed as an

adverse event in the prescribing information, and there is no new safety signal identified in the narratives of the SAEs.

Narratives of the SAEs were also reviewed for the entire ISS and open-label extension studies. There were no treatment-emergent SAEs with IV use in study EP0060. In this pediatric age group, there were additional SAEs in the open-label extension studies, with a total of 8 patients reporting an SAE of pneumonia, and 5 patients each reporting SAEs of convulsion and status epilepticus.

Reviewer's comment: There were 5 reports each of worsening convulsions or status epilepticus. Although it is difficult to know if any of these were drug-related or merely due to the patient's underlying condition, the majority did not lead to discontinuation. Worsening convulsions is already listed as a potential adverse event in the prescribing information. No new safety signal is identified.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were two patients in SP0967 who had AEs that led to discontinuation, one with the appearance of idiopathic generalized epilepsy, and one with an AE of sinus bradycardia. Brief narratives are described below:

(b) (6), *primary generalized epilepsy*

1.6-year-old male (weight 9.9 kg), with history of developmental delay and epilepsy on concomitant diazepam. Initiated LCM in study on (b) (6), and experienced a nonserious AE of pharyngitis. The patient then developed a diagnosis of primary generalized epilepsy on (b) (6), based on new seizure type, 26 days after drug initiation. The patient was withdrawn from the study and switched to commercial LCM. Final visit was (b) (6). Event was considered mild and not related by the investigator.

(b) (6), *sinus bradycardia*

2-year-old female (weight 7.6 kg), with a history of blindness, cerebral palsy, and epilepsy, with a seizure frequency of 35.8 seizures per day. She was on concomitant levetiracetam and topiramate. She initiated LCM on (b) (6) and experienced a nonserious AE of sinus bradycardia during the Maintenance Period on (b) (6) 29 days after drug initiation. The event was considered mild and not related to study drug by the investigator. The patient was receiving 6 mg/kg/day at time of event. Dose had been decreased from 8 mg/kg/day. Patient's ECGs were reviewed, and she did have a left anterior hemiblock sinus tachycardia on ECG on the day of study drug initiation. Her heart rate ranged from 75-123 with the lowest recorded heart rate documented at baseline prior to study drug. However, she was discontinued from the study for the AE of sinus

bradycardia.

There were no AEs that led to discontinuation in Study EP0060, safety and tolerability of intravenous LCM. In the open-label extension studies, there were 10 additional discontinuations secondary to an adverse event. There was 1 patient each that discontinued due to skin rash, drug-induced hepatotoxicity, aspiration pneumonia, pulmonary failure, sinus bradycardia, and 5 patients who discontinued for PTs of seizure (seizure, worsening of seizure frequency, or status epilepticus).

Reviewer's comment: The events above of sinus bradycardia and appearance of a primary generalized seizure type do not appear to be drug-related although both are already described in product labeling as potential adverse events. Worsening of seizures in the open-label extension studies may be attributed to drug or underlying seizure disorder, but there are no new safety signals that are unique to this patient population.

8.4.4. Significant Adverse Events

A total of 7 patients had AEs graded as severe throughout the study (3 on LCM and 4 on placebo). The 3 patients on LCM who had severe AEs reported events of vomiting, chronic pneumonia, and irregular sleep phase/somnolence in one patient each. The placebo patients with severe AEs reported aspiration pneumonia, femur fracture, enteritis, fever, and upper respiratory tract infection. There were no severe TEAEs in the IV study, Study EP0060.

AEs of Special Interest (SP0967)

Sinus Bradycardia
There were 2 patients who had a TEAE of sinus bradycardia. One patient is described above in Section 8.4.3 as it led to discontinuation. The other patient with sinus bradycardia is described here in more detail.

(b) (6), *sinus bradycardia*

2.58-year-old male (weight 15.2 kg), with significant past medical history including history of cardiac ventricular disorder, h/o cardiac resuscitation, h/o sick sinus syndrome, and h/o hypoxic-ischemic encephalopathy, cerebral palsy, and metabolic cardiomyopathy on concomitant oxcarbazepine, valproic acid, bromisoval, phenobarbital, caffeine, and papaverine. The patient initially received placebo, and then entered the Transition Period on (b) (6) He experienced first degree AV block on (b) (6) prior to first dose of study drug. He also experienced a nonserious AE of sinus bradycardia on (b) (6) 9 days after initiation of LCM. The event was considered mild but felt to be related to study drug. Per vital signs documented, heart rate was noted to be low (67) on

(b) (6) as well, prior to study drug initiation, but was as low as 62 at the time of the documented AE. The event did not lead to drug discontinuation.

Reviewer's comment: The two events of sinus bradycardia were mild and may or may not have been related to study drug. Both patients appeared to also have low heart rates at other documented times besides the time of the AE report of sinus bradycardia. First degree heart block and bradycardia are a well-documented side effect of LCM.

Decreased Appetite
There were 3 AEs of decreased appetite in Study SP0967, two of which were reported on patients on placebo, and one which occurred in a patient on LCM (who also had an SAE of vomiting, see narrative above in Section 8.4.2).

Reviewer's comment: Although there has been interest in decreased appetite as an adverse event in pediatric patients receiving LCM, there is no evidence in this double-blind placebo-controlled study of a signal for decreased appetite in the youngest patients. It is possible that, given the young age of the patients, parents and caregivers may not be aware of or able to accurately describe a decreased appetite.

Irritability/Aggression
Irritability and aggression were AEs of interest given the age range of the patient population. There were 13 reports of irritability (5 on placebo, 7 LCM, and 1 patient who received placebo but developed symptoms on the first day of LCM in the Transition period). Four patients (2 placebo, 2 LCM) reported aggression.

Reviewer's comment: There were a number of patients who reported irritability and aggression in the double-blind treatment period, but the events were equally distributed between the placebo and treatment arms. There is no new safety signal identified.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Overall, in Study SP0967, TEAEs were reported in 73 patients receiving placebo (58%) and 66 patients receiving LCM (52 %). During the "Treatment Period" which consisted of the Titration and Maintenance Period, TEAEs were reported in 65 patients receiving placebo(51%), and 57 patients receiving LCM (44%). The most common TEAEs that occurred in ≥ 2 % of the patients on LCM and greater than placebo are outlined below in Table 11.

Table 11 Common TEAEs that occurred in ≥ 2% of the patients on LCM and greater than placebo (SS)

Adverse Event	LCM (N = 128) n (%)	Placebo (N = 127) n (%)	Risk Difference %
Nervous System Disorders			
Somnolence	15 (12)	4 (3)	9

Irritability	7 (5)	5 (4)	2
Gastrointestinal Disorders			
Liver function test abnormal*	6 (5)	1 (2)	3
Vomiting	7 (5)	4 (3)	2

Source: Reviewer-derived table from SP0967 ADAE dataset, for AEs that occurred during Titration and Maintenance Period only
*SS = safety Set; LCM = lacosamide, * includes recoded terms to combine liver function test abnormal with alanine transferase increased*

Reviewer's comment: The common TEAEs reported during the study were compared to placebo and the above AEs somnolence, vomiting, and liver function test abnormal, all of which are already reported in the prescribing information and are similar to what has been seen in previous studies. Irritability was reported commonly in both the treatment and placebo arms. There was no evidence of any unique AEs in this youngest population of patients.

8.4.6. Laboratory Findings

Overall, there were no consistent or clinically relevant changes from baseline in mean hematology values or mean clinical chemistry values. The incidence of treatment-emergent markedly abnormal hematology values were low for most parameters, with the exception of a few incidences of markedly high leukocytes, lymphocytes, and neutrophils. These were abnormal more frequently in the placebo arm than the LCM arm. There were no serious hematologic TEAEs, and the only TEAE to occur in more than 1 patient receiving treatment was eosinophilia. None led to treatment discontinuation.

The incidence of treatment-emergent markedly abnormal chemistry values was overall low with the exception of markedly low bicarbonate (8.6% in LCM and 4.7% in placebo), markedly high triglycerides (4.7% LCM, 3.1% in placebo) and high GGT (3.1% in both LCM and Placebo treatment arms). The only TEAE related to chemistry seen in more than 1 patient receiving treatment were ALT increased and LFT abnormal, which is already included in the prescribing information. None of the chemistry-related TEAEs were serious and none led to discontinuation. No patient met potential drug-induced liver injury (pDILI) criteria.

Reviewer's comment: There were no new laboratory-related safety signals identified with the use of LCM in this young pediatric population. LFTs were increased in a few patients but none were serious or led to discontinuation. Elevation of LFTs is already included in the prescribing information for LCM.

8.4.7. Vital Signs

There were no clinically relevant changes from baseline in vital sign parameters. There was one patient with sinus bradycardia (outlined above in Section 8.4.4). An additional patient

experienced sinus bradycardia during the Transition period (Section 8.4.4). There were no patients who experienced a TEAE related to markedly abnormal vital signs.

In the open-label extension study SP848, there were overall low incidence of TEAEs related to abnormal vital signs, and the majority were mild except for 1 moderate event of blood pressure increased, 1 severe event of weight decreased, and 2 serious events of bradycardia and weight decreased. None led to discontinuation. No marked bradycardia was reported.
In EP0034, there was one reported event of bradycardia. There were some markedly abnormal vital sign values in blood pressure, pulse, and weight, but none appears to be clinically relevant. One patient each reported TEAEs of hypotension, tachycardia, heart rate increased, and hyperthermia, with 2 patients reporting TEAEs of hypertension.

Reviewer's comment: There were no new vital sign-related safety signals identified with the use of LCM in this young pediatric population. Bradycardia is a known risk associated with LCM and is described in Section 8.4.4 above.

8.4.8. Electrocardiograms (ECGs)

There were no clinically relevant changes from baseline in mean or median ECG findings considered to be related to LCM. Bradycardia was noted as above. One patient in the placebo treatment arm had a post-baseline clinically significant ECG result.

In the open-label study EP0034, there was a patient less than 4 years of age who experienced a TEAE of Brugada syndrome on Day 98. The patient was receiving LCM 10 mg/kg/day at the time. The patient had bronchitis with a fever and an ECG was performed at a routine follow-up visit. The ECG results were consistent with Brugada syndrome. The patient remained in the study because the patient was asymptomatic. The TEAE was considered mild in intensity and not serious and did not lead to withdrawal from the study.

Reviewer's comment: There were no clinically significant ECG changes noted with the use of LCM in this young pediatric population.

8.5. Analysis of Submission-Specific Safety Issues

In Studies SP0967 and EP0060, there were no TEAEs of memory impairment, amnesia, or cognitive disorder, no TEAEs of psychotic disorders, no TEAEs of suicidal ideation, behavior, or attempts, and no TEAEs related to body weight changes.

Other submission-specific safety issues including bradycardia, behavior (aggression, irritability), and decreased appetite are outlined above in Section 8.4.4.

8.6. Safety Analyses by Demographic Subgroups

Table 12 Analysis of All TEAEs/SAEs by Demographic Subgroup (SP0967 Safety Set)

	Sex		Age				Race			
	M N = 146 n (%)	F N =109 n (%)	≥ 1 mos to < 6 months N= 16 n (%)	≥ 6 mos to < 1 year N = 31 n (%)	≥ 1 year to < 2 years N =74 n (%)	≥ 2 years to < 4 years N =134 n (%)	White N = 195 n (%)	Black N =2 n (%)	Asian N = 29 n (%)	Other* N = 29 n (%)
TEAEs	81 (55)	58 (53)	6 (37)	17 (55)	34 (46)	82 (61)	102 (52)	0	22 (76)	15 (52)
SAEs	9 (6)	3 (3)	0	1 (3)	3 (4)	8 (6)	12 (6)	0	0	0

**Other races = American Indian, Hispanic, Other/Mixed*
Source: Reviewer analysis of SP0967 ADSL and ADAE datasets of Safety Set, Titration and Maintenance treatment period only

Reviewer's comment: Overall, in Study SP0967, there were no clinically significant differences in the incidence of TEAEs or SAEs by age, sex, or race. The small patient numbers in each group make it difficult to draw any conclusions. However, there was noted a slightly decreased incidence of TEAEs in the youngest age, and a higher incidence among the Asian race group; given the small patient numbers, no significant conclusions can be drawn.

8.7. Safety in the Postmarket Setting

8.7.1. Safety Concerns Identified Through Postmarket Experience

The Applicant presented an analysis of postmarketing reports of the use of LCM in pediatric patients less than 4 years of age since initial approval in August 2008. The UCB Global Safety Database was cumulatively searched for all postmarketing cases with the use of LCM in any dose and formulation in pediatric patients less than 4 years of age, including neonates. The safety database identified 428 postmarketing cases. When possible, the analysis was compared to pediatric patients 4 years to less than 17 years of age.

Of the 428 reported cases, 77 (18%) were serious, and 15 (1.9%) were fatal. Approximately 25% of the cases came from the United States. The most frequently reported adverse events in the pediatric patients aged 1 month to less than 4 years of age were similar to those reported in older pediatric patients. Seizure was most common (8.4%), intentional product misuse (5.3%), drug ineffective (4.2%), and multiple-drug resistance (2.3%). Multiple-drug resistance was reported with increased frequency in this population compared to older pediatric patients.

There were 8 cases with a fatal outcome were reviewed. There were no reports of sudden unexpected death in epilepsy patients (SUDEP). There were not a lot of details on some of the cases, but the majority seemed unrelated to treatment with LCM. One patient reported in the

literature died from status epilepticus and associated multi-organ failure and brain herniation shortly after withdrawal of LCM.

Reviewer's comment: The fatal cases were confounded with limited medical history to make any reasonable conclusions. Most of the cases were reported with alternative cause of death. The only one reasonably linked to LCM is the above noted literature report of the 3 year old who may have died as a result of complications of status epilepticus related to withdrawal of LCM. It is already in the prescribing information to withdraw LCM gradually to minimize any worsening of seizure frequency.

The global safety database was also searched specifically for cardiac conduction and ECG-related events. There were 4 cases identified, one of which was fatal and was reviewed above. The other 3 cases included a premature infant with shortened PR interval, a patient with bradycardia in the context of a tonic seizure, and another patient who had bradycardia, also associated with seizure but worsened bradycardia when LCM dose was increased.

Reviewer's comment: The above-described cases of cardiac conduction abnormalities do not provide a new safety signal in this population, and there is no evidence of any unique safety cardiac concerns in the youngest patients.

There were also 3 reports of hepatotoxicity-related events in the global safety database, with minimal details reported. One patient developed increase in hepatic enzyme levels without any clear medical cause, which is already described in the prescribing information. There were no cases of multiorgan hypersensitivity and drug reaction with eosinophilia and systemic symptoms (DRESS) or severe cutaneous adverse reactions in this age group.

Reviewer's comment: Overall the review of the postmarketing database did not reveal any new safety concerns or events that were unique to pediatric patients age 1 month to less than 4 years of age.

8.7.2. Expectations on Safety in the Postmarket Setting

The postmarket use of LCM in pediatric patients 1 month to less than 4 years of age is expected to be similar to the current off-label use, although some prescribers may be more comfortable using it in the youngest pediatric population once it has the approved indication, so overall use may become slightly more frequent in this age group. Routine pharmacovigilance is recommended.

8.7.3. Additional Safety Issues From Other Disciplines

None.

8.8. Integrated Assessment of Safety

Overall, the most frequently reported TEAEs in Study SP0967 were consistent with the known safety profile of LCM in the treatment of older pediatric patients and adults. The most commonly reported adverse events seen with LCM were somnolence and vomiting. There were no new safety signals identified that were unique to this young patient population. Additionally, the safety of intravenous LCM in 26 pediatric patients greater than or equal to 1 month to less than 4 years of age was similar to that in pediatric patients greater than 4 years of age.

9. Labeling Recommendations

9.1. Prescription Drug Labeling

The labeling has not been finalized at the time of completion of this review. See final approved labeling.

9.2. Nonprescription Drug Labeling

Not applicable.

10. Risk Evaluation and Mitigation Strategies (REMS)

None required.

11. Postmarketing Requirements and Commitments

This current supplement is intended to fulfill PREA PMR 2774-1, PREA PMR 3288-1, and PREA PMR 3293-1 as outlined above in Table 2.

There are four outstanding PREA requirements to study an [redacted] (b) (4) (loading dose) that will be addressed by Study EP0147: PREA PMRs 2744-2, 2744-3, 3957-1, and 3957-2, as described below in

Table 13 and

[redacted] (b) (4)

Table 13 Overview of VIMPAT PREA requirements for [redacted] (b) (4) (POS)

PREA Number	PREA description	UCB studies
2774-2[a] applies to VIMPAT tablet (NDA 22253), VIMPAT injection (NDA 22254), and VIMPAT oral solution (NDA 22255)	A study that will examine safety and tolerability of an oral loading dose that will allow a more rapid achievement of the final recommended therapeutic dose in pediatric patients ≥1 month to <17 years of age **Study Completion: Sep 2020** **Final Report Submission: Mar 2021**	EP0147 CL0447 Part IV
2774-3 [a] applies to VIMPAT tablet (NDA 22253), VIMPAT injection (NDA 22254), and VIMPAT oral solution (NDA 22255)	A study that will examine safety and tolerability of an intravenous loading dose that will allow a more rapid achievement of steady-state exposures of the final recommended therapeutic dose in pediatric patients ≥1 month to <17 years of age. **Study Completion: Mar 2021** **Final Report Submission: Sep 2021**	EP0147

NDA=New Drug Application; PREA=Pediatric Research Equity Act

[a] PREA requirement issued in 29 Aug 2014 approval letter of NDA 022253/S-026 and S-027, NDA 022254/S-019 and S-020, and NDA 022255/S-012, S-013 and S-022

Table 14 Overview of VIMPAT PREA requirements for Alternate Initial Dose (PGTCS)

PREA Number	PREA description	UCB studies
3957-1[a] applies to VIMPAT tablet (NDA 22253), VIMPAT injection (NDA 22254), and VIMPAT oral solution (NDA 22255)	A study that will examine safety and tolerability of an oral loading dose of Vimpat (lacosamide) that will allow a more rapid achievement of the final recommended therapeutic dose in pediatric patients 4 to <17 years of age. **Study Completion: Sep 2020** **Final Report Submission: Mar 2021**	EP0147 CL0447 Part IV
3957-2[a] applies to VIMPAT tablet (NDA 22253), VIMPAT injection (NDA 22254), and VIMPAT oral solution (NDA 22255)	A study that will examine safety and tolerability of an intravenous loading dose of Vimpat (lacosamide) that will allow a more rapid achievement of steady-state exposures of the final recommended therapeutic dose in pediatric patients 4 to <17 years of age. **Study Completion: Sep 2020** **Final Report Submission: Mar 2021**	EP0147

NDA=New Drug Application; PREA=Pediatric Research Equity Act

[a] PREA requirement issued in 16 Nov 2020 approval letter of NDA 022253/S-046 and S-048, NDA 022254/S-036 and S-038, and NDA 022255/S-027 and S-030

12. Appendices

12.1. References

See footnotes throughout.

12.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): SP0967, SP0848, EP0034

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 344 (SP0967)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4 (SP0848 only)		
If there are investigators with disclosable financial interests/arrangements, identify the		

number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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/s/

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