CLINICAL REVIEW

Application Type	NDA efficacy supplement
Application Number(s)	022253 (S-48) / 022254 (S-38) / 022255 (S-30)
Priority or Standard	Standard
Submit Date(s)	April 30, 2020
Received Date(s)	April 30, 2020
PDUFA Goal Date	February 28, 2021
Division/Office	Division of Neurology 2/ Office of Neuroscience
Reviewer Name(s)	Emily R. Freilich, MD
Review Completion Date	October 23, 2020
Established/Proper Name	Lacosamide
(Proposed) Trade Name	Vimpat
Applicant	UCB, Inc
Dosage Form(s)	injection
Applicant Proposed Dosing Regimen(s)	1-2 mg/kg/day, up to maximum 8 mg/kg/day - 12 mg/kg/day
Applicant Proposed Indication(s)/Population(s)	For extension of the use of the intravenous formulation for temporary replacement of oral dosing for pediatric patients ≥ 4 to < 17 years of age
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Intravenous formulation for the temporary replacement of oral dosing in pediatric patients 4 years and older

Table of Contents

Table of Tables

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
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
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
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
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
SUDEP	sudden unexpected death in epilepsy patients
TEAE	treatment emergent adverse event
ULN	upper limit of normal
VNS	vagal nerve stimulator
VPA	valproic acid

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) in patients 4 years and older in both tablet and oral solution, and in patients 16 years and older in injection for infusion. 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 were added in 2014. The indication was extended down to 4 years of age in 2017 for oral formulations only. The Applicant has a PREA Post Marketing Requirement (PMR) to study the safety and tolerability of the intravenous formulation in pediatric patients.

The current submission is in response to the outstanding PREA PMR and the Applicant proposes to expand the current indication for LCM (tradename Vimpat) intravenous solution to pediatric patients 4 years and older. Of note, supplemental NDA sNDA 022253 (S-46)/ 022254 (S-36)/ 022255 (S-27) is concurrently under review for addition of a new indication of the adjunctive treatment of primary generalized tonic clonic seizures (PGTCS) in patients (b) (4) 4 years and older for all formulations.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The submission does not contain a new efficacy study for review. The effectiveness of intravenous LCM for the adjunctive treatment of seizures in pediatric patients 4 years to < 17 years old is established through bioequivalence with the oral formulation, for which efficacy has previously been established in the treatment of POS (sNDA 022253(S-39)/ 022254 (S-30)/ 022255(S-22)), and is concurrently established in the treatment of PGTCS (sNDA 022253 (S-46)/ 022254 (S-36)/ 022255 (S-27)).

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

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. If patients are on an effective oral treatment regimen, it may be hard to manage their seizures in the event of intermittent illnesses, surgeries, or other hospitalizations that make it difficult for them to take medications by mouth.

LCM was previously approved as VIMPAT for the treatment of partial-onset seizures in adults in 2008 in both oral tablet and intravenous formulations. The oral formulations were extended down to patients age 4 years and older in 2017, and the Applicant had a PREA PMR to study the safety and tolerability and pharmacokinetics (PK) of the intravenous formulation in pediatric patients. The current submission includes a single, open-label, safety and PK study (Study EP0060) in 103 patients age 1 month to less than 17 years of age. Effectiveness of intravenous LCM is established through bioequivalence with the oral formulation, and the indication is for the temporary replacement of oral LCM when patient is unable to tolerate PO medications.

The safety profile of LCM is well-characterized in adults and in the oral formulation in pediatric patients through prior controlled studies and extensive postmarketing history since initial approval. The safety data from the submitted study includes 77 patients 4 years to less than 17 years of age who tolerated up to 10 infusions of intravenous LCM, with the majority of patients receiving 1-2 infusions. The safety data did not reveal any new safety signals, and there were very few adverse events reported during the study. Only 4 patients received infusion over a duration shorter than 30 minutes, with the shortest infusion time of 21 minutes. Therefore, there is insufficient data to recommend infusion times less than 30 minutes in pediatric patients, as is indicated in adults when clinically necessary.

Intravenous LCM is a safe and bioequivalent substitute for oral LCM in the treatment of pediatric patients with epilepsy who are unable to tolerate oral medications due to recent seizure, intercurrent illness, or prior to surgery. The adverse reactions, while not seen in this study, are expected to be similar to those observed in the adult studies of intravenous LCM.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Seizures in pediatric patients may be refractory and difficult to treat. • Both partial-onset seizures and primary generalized tonic clonic seizures are common in pediatric patients, although partial-onset seizures typically appear younger than primary generalized tonic-clonic seizures. • Refractory seizures increase the risk of life-threatening conditions such as status epilepticus, as well as the risk for sudden death. • Patients often need temporary substitution for seizure medications when unable to tolerate oral treatment due to illness, seizure, or surgery.	There is a need for intravenous seizure medications that may be a temporary replacement for oral medications when pediatric patients are unable to tolerate oral treatments.
Current Treatment Options	• There is not an approved intravenous substitute for oral lacosamide in pediatric patients.	The ability to substitute a patient's oral medication with a bioequivalent IV formulation is rare, but may be vital to maintaining adequate seizure control.
Benefit	• Intravenous LCM is bioequivalent to the oral formulations. • Oral formulations are effective in treatment of pediatric patients age 4 years and older with partial-onset seizures and primary generalized tonic-clonic seizures (the latter being approved contemporaneously with this action).	Intravenous LCM is an acceptable substitute for the treatment of seizures in pediatric patients who are unable to take medication by mouth.
Risk and Risk Management	• The safety profile of LCM is well-characterized in adults and pediatric patients in the oral formulation. • The safety of intravenous LCM is well-established in adults. • The submitted open-label study of 77 patients receiving intravenous LCM to initiate treatment with LCM or as replacement for oral dosing, did not demonstrate any serious adverse events or acute infusion reactions.	Intravenous LCM was safely administered and well-tolerated by 77 pediatric patients age 4 years to less than 17 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 receiving intravenous LCM.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• A total of 4 patients received infusions that were shorter than 30 minutes in duration, with a range of 21-28 minutes. No patients required or received a faster infusion time of 15 minutes in the study.	There is insufficient data to recommend infusion times less than 30 minutes in pediatric patients.

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

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]. In an analysis of a pediatric database in Norway, 19% of children with epilepsy were found to have primary generalized tonic-clonic seizures[6].

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.[7,8]. Uncontrolled epilepsy in the pediatric patients, especially in those patients with 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] Aaberg KM, Surén P, Søraas CL, et al. Seizures, syndromes, and etiologies in childhood epilepsy: The International League Against Epilepsy 1981, 1989, and 2017 classifications used in a population-based cohort. Epilepsia. 2017 Nov;58(11):1880-1891.
[7] Baranowski CJ. The quality of life of older adults with epilepsy: A systematic review. Seizure. 2018 Aug;60:190-197.
[8] 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.[9] 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[10]. 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[11]. 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[12].

As opposed to POS, PGTCS have apparent clinical or EEG onset in both hemispheres of the brain, with no clear focus or foci. PGTCS are associated with idiopathic generalized epilepsy and several generalized epilepsy syndromes. Onset of PGTCS typically starts in older children, adolescents, and young adults, but does present in children as young as 2 years. One critical EEG hallmark of a susceptibility to generalized seizures, including PGTCS, are well-formed generalized spike-wave discharges.

Pediatric patients with epilepsy may intermittently require a temporary substitution of their oral medications due to illness, seizure, or surgery. Alternatively some patients with new-onset seizures may need to initiate a new medication while unable to tolerate medications by mouth.

2.2. Analysis of Current Treatment Options

A total of 16 drugs are approved for use in the treatment of seizures in pediatric patients with varying degrees of supporting efficacy data. However, there are more limited treatments that are available in both oral and intravenous formulations for pediatric patients with epilepsy as noted in the below table. Of note, Fosphenytoin is another intravenous product approved for use in pediatric patients, as it is a water-soluble phenytoin product administered intravenously approved in 1996, but is only indicated for status epilepticus and the prevention and treatment of seizures occurring during neurosurgery or short-term oral replacement of phenytoin. Phenytoin itself is included in the table, and Fosphenytoin is considered a safer alternative to the use of intravenous phenytoin.

---

[9] Nickels KC, Zaccariello MJ, Hamiwka LD, Wirrell EC. Cognitive and Neurodevelopmental Comorbidities in Paediatric Epilepsy. Nat Rev Neurol. 2016 Aug; 12(8):465-476.
[10] 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
[11] Fisher RS. The New Classification of Seizures by the International League Against Epilepsy 2017. Curr Neurol Neurosci Rep (2017) 17: 48
[12] Chang BS and Lowenstein DH. Mechanisms of Disease: Epilepsy. NEJM (2003) 349;13

Table 1 Summary of Treatments Available for Pediatric Epilepsy in Intravenous Dosing Form

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	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.
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
Phenytoin (PHT)	Indicated for the treatment of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery, or as a substitute for oral phenytoin. Oral phenytoin is indicated for the treatment of tonic-clonic and psychomotor (temporal lobe) seizures.	1953	IV, every 6-8 hours	Not available	Boxed warning for Cardiovascular Risk associated with rapid infusion. Additional warnings for withdrawal precipitated seizure/status epilepticus, serious dermatologic reactions, DRESS/multiorgan hypersensitivity, hypersensitivity, hepatic injury, hematopoietic complications, local toxicity, renal or hepatic impairment/hypoalbuminemia, exacerbation of porphyria, teratogenicity, hyperglycemia, concern for slow metabolizers who may have dose-related CNS toxicity, related to confusional states and cerebellar dysfunction at supra-therapeutic levels.
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 ≥ 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, with post-marketing requirements to complete a separate safety and tolerability study of the intravenous formulation in pediatric patients.

The submitted study, EP0060 was designed to address the PREA PMRs pertaining to NDA 022254 as noted below. The present supplement aims to partially fulfill PREA PMR 2774-1 for patients 4 years of age and older [redacted] (b) (4) The study also fulfills PREA requirement 3293-2 for deferred studies for patients with POS in pediatric patients 4 years to < 17 years assigned to the intravenous formulation.

Table 2 Outstanding PREA PMRs for NDA 022254

PREA Number	PREA description
2774-1[a]	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 PK of LCM and its metabolite using PPK approach in this population.
3293-1[b]	Deferred pediatric studies under PREA for the treatment of partial-onset seizures in pediatric patients ages 1 month to <4 years.
3293-2[b]	Deferred pediatric studies under PREA for the treatment of partial-onset seizures in pediatric patients ages 4 years to <17 years.

iv= intravenous; LCM=lacosamide; NDA=New Drug Application; PK=pharmacokinetics; POS=partial-onset seizures; PPK=population pharmacokinetic; PREA=Pediatric Research Equity Act

[a] PREA requirement issued on 29 Aug 2014 as part of the approval letter of NDA 022253/S-026 and S-027, NDA 022254/S-019 and S-020, and NDA 022255/S-012 and S-013, and deferred as per deferral request (NDA 022254/S-0186) granted on 16 Nov 2017.

[b] PREA requirement issued on 28 Oct 2008 as part of the approval letter of NDA 022253 and NDA 022254. PREA requirement revisited on 03 Nov 2017 in the approval letter of NDA 022253/S-039, NDA 022254/S-030, and NDA 022255/S-022

APPEARS THIS WAY ON ORIGINAL

3.2. Summary of Presubmission/Submiss

The original protocol for Study EP0060 was dated 16 Dec 2014. There were three subsequent protocol amendments that are summarized briefly below.

- In 2015, prior to the start of patient enrollment, Protocol Amendment 1 clarified the

study design and which patients qualified for enrollment into the study, as well as the PK assessments requested by the Agency.

- In November 2016, Protocol Amendment 2 allowed for enrollment of patients who were already on a stable dose of LCM through other open-label pediatric studies or by their prescribing physician, as well as patients initiating LCM as adjunctive treatment with IV LCM. It also allowed for patients to continue with oral LCM treatment in the ongoing open-label study SP848 if clinically appropriate. This amendment merged the age cohorts ≥8 to < 12 years of age with ≥ 12 to < 17 years of age into a single cohort spanning ≥ 8 to < 17 years of age.

- Protocol Amendment 3 in April 2018 lowered the age of study participants from (b) (4) years to ≥ 1 month of age to maximize the participant pool in evaluating the safety of IV LCM and to include age stratification within Cohort 2 in order to be the most informative with regard to safety and PK. This amendment also increased enrollment from (b) (4) to 100 participants to reflect inclusion of patients down to 1 month of age.

Amendment 3 was justified by published literature and postmarketing data on off-label use to justify the Applicant's inclusion of the youngest patients.

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.

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

The proposed doses are the same as the already approved oral doses for treatment of partial-onset seizures and primary generalized tonic clonic seizures. PK data was submitted as part of the results of Study EP0060. See Dr. Adarsh Gandhi's Clinical Pharmacology review of the proposed doses and the required PK and population PK analyses.

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

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						
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 < 1 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 currently receiving prescribed oral LCM from commercial supply Initiating iv LCM (IIL): patients not currently receiving LCM and receiving first dose in the study	22 sites in 5 countries (US, Ukraine, Poland, Hungary, Italy)

5.2. Review Strategy

This clinical review will primarily examine Study EP0060, an open-label PK safety and tolerability study of the use of intravenous LCM in pediatric patients 1 month to < 17 years of age. 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 the intravenous formulation was initially approved in 2008.

I will perform my own safety analyses based on data provided by the Applicant from Study EP0060. Further supportive safety information will be reviewed from the postmarketing database. Safety analyses will focus on safety in patients 4 years and older, as LCM is currently not approved in patients < 4 years of age for any indication.

6. Review of Relevant Individual Trials Used to Support Efficacy

Not applicable. No independent efficacy studies were completed or reviewed for this supplement review.

7. Integrated Review of Effectiveness

As noted above, efficacy was established through pharmacokinetic establishment of bioequivalence to the oral formulation. No independent efficacy studies were completed or reviewed for this supplement review.

Please see the clinical pharmacology review for further detail.

8. Review of Safety

8.1. Safety Review Approach

Safety was reviewed for the use of the intravenous formulation in pediatric patients from Study EP0060, which is described briefly below.

Study EP0060, as noted in Table 3 above, is a Phase 2/3 open-label study to investigate the safety and tolerability of intravenous LCM in children ≥ 1 month to < 17 years of age with epilepsy. The study enrolled 103 patients with both POS and PGTCS. Patients were eligible for enrollment in EP0060 through 3 different mechanisms:

- Open-label LCM (OLL) patients: Patients were receiving oral LCM as adjunctive or monotherapy as a participant in an open-label long-term study

- Prescribed-LCM (RxL) patients: Patients who were receiving prescribed oral LCM from commercial supply (e.g. Vimpat) as adjunctive or monotherapy.

- Initiating IV LCM (IIL) patients: Patients who were not receiving LCM and received IV LCM as adjunctive treatment in EP0060. Initiation of LCM monotherapy was not permitted in IIL participants.

After completion of the study, eligible study participants from the RxL and IIL groups did have the option to continue open-label LCM treatment in the ongoing open-label extension study SP848.

EP0060 was designed to include 2 age-based cohorts with Cohort 1 including at least 40 patients who were ≥ 8 to < 17 years of age and Cohort 2 including approximately 44 patients who were ≥ 1 month to < 8 years of age. Within Cohort 1 at least 20 patients were to be ≥ 8 to < 12 years of age, and at least 20 patients were to be ≥ 12 to < 17 years of age. Within Cohort 2, attempts were to be made to enroll 20 patients ≥ 4 to < 8 years of age, 12 patients ≥ 2 to < 4 years of age, and 12 patients ≥ 1 month to < 2 years of age.

The study was designed so that the screening, baseline, treatment period, and final visit could occur in 1 study day, provided patients only required a single intravenous infusion. However, the screening and baseline period could last up to 7 days as needed to confirm patient eligibility or prepare for elective dosing. Patients could receive multiple infusions, approximately 12 hours apart, for up to 5 days (10 total doses) if clinically required, or up to 2 intravenous infusions if administration was elective. Dosing for patients already receiving oral LCM (groups OLL and RxL) was the same as the patient's current stable daily dose of oral LCM (2-12 mg/kg/day, maximum 600 mg/day). For patients initiating LCM (IIL patients), the starting dose was 1 mg/kg/day twice daily or 50 mg twice daily (weight ≥ 50 kg).

Finally, the study began with Cohort 1, and the first 20 patients received the infusion for a duration of 30-60 minutes. After completion of the first 20 patients, an Independent Data Monitoring Committee (IDMC) reviewed the safety and tolerability data from the patients and recommended that additional patients could be enrolled and could receive the infusion at a faster infusion time of 15-30 minutes if deemed medically appropriate by the Investigator. Cohort 2 was also initiated. For Cohort 2, the first 20 patients also received an infusion of 30-60 minutes. After the first 20 patients were enrolled in Cohort 2, the IDMC reviewed the safety data again and recommended that the final patients could be enrolled, but recommended only the 30-60 minute infusion duration be used as no earlier patients had clinical need requiring a dose infusion time of 15-30 minutes.

This review will focus primarily on review of patients 4 to < 17 years of age, as studies of LCM in patients with POS < 4 years of age are ongoing and LCM is not currently approved in any formulation or for any indication in patients < 4 years of age. However, demographic and AE information in patients < 4 years of age is included for completeness.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

There were 103 total patients treated in the study. All patients completed the study with no treatment discontinuations. Of these patients, 77 patients were age 4 years or older. The baseline demographic and eligibility characteristics are outlined below in Table 5. The total exposures by age and infusion duration are in Table 4. No patients discontinued from the study.

Table 4 Total Exposure by Age and Infusion Duration

	Age Distribution			
	≥ 1 mo to < 4 years N = 26	≥ 4 to < 12 years N = 42	≥ 12 to < 17 years N = 35	Total N = 103
Number of infusions received				
1 infusion	13	34	32	79
2 infusions	13	7	0	20
≥ 3 infusions*	0	1	3	4
Total Number of Infusions	39	58	55	152
Infusion Duration (Number of Infusions)				
21 to < 30 minutes	2	0	2	4
30 to < 40 minutes	28	31	26	85
40 to < 50 minutes	1	14	16	31
50 to 60 minutes	8	13	11	32

Source: Reviewer-derived table from EP0060 ADEX dataset

** 1 patient received 3 infusions, and 3 patients received 10 infusions each*

8.2.2. Relevant characteristics of the safety population:

Table 5 Demographics and Baseline Characteristics of Safety Population

Demographic Parameters	LCM ≥ 1 mos to < 4 years N = 26 n (%)	LCM ≥ 4 to < 17 years N = 77 n (%)	Total LCM N = 103 n (%)
Sex			
Male	12 (46)	34 (44)	46 (45)
Female	14 (54)	43 (56)	57 (55)
Age (years)			
Mean (SD)	2.1 (1.4)	10.7 (3.7)	8.6 (5.0)
Median	2.4	11.2	8.5
Min, Max	0.17, 3.9	4.1, 16.6	0.17, 16.6
Age Group			
≥ 1 mo to < 4 years	26 (100)	0	26 (25)
≥ 4 to < 8 years	0	22 (29)	22 (21)
≥ 8 to < 12 years	0	20 (26)	20 (19)
≥ 12 years	0	35 (45)	35 (34)
Weight (kg)			
Mean (SD)	11.1 (4.3)	41.6 (22.3)	33.9 (23.5)
Median	12.1	33.3	27.2
Min, Max	4.8, 18.5	14.7, 111.9	4.8, 111.9
Race			
White	26 (100)	70 (91)	96 (93)
Black or African American	0	5 (7)	5 (5)
Asian or Other	0	2 (2)	2 (2)
Ethnicity			
Hispanic or Latino	1 (4)	9 (12)	10 (10)
Not Hispanic or Latino	25 (96)	68 (88)	93 (90)
Region			
United States	0	26 (34)	26 (25)
Europe*	26 (100)	51 (66)	77 (75)
Enrollment Type			
IIL	24 (92)	50 (65)	74 (72)
OLL	0	3 (4)	3 (3)
RxL	2 (8)	24 (31)	26 (25)
Assigned Infusion Duration			
15-30 minutes	5 (19)	17 (22)	22 (21)
30-60 minutes	21 (81)	60 (78)	81 (79)
Total Number Infusions			
1 infusion	13 (50)	66 (86)	79 (77)
2 infusions	13 (50)	7 (9)	20 (19)
>2 infusions**	0	4 (5)	4 (4)

Source: Reviewer-derived from EP0060 ADSL dataset
LCM = lacosamide; IIL = initiating LCM; OLL = receiving LCM in an open-label study; RxL = prescribed LCM
** Europe includes Ukraine, Poland, Hungary, and Italy*
*** 1 patient received 3 infusions, and 3 patients received maximum 10 infusions*

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 safety database for the support of IV use in pediatric patients 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 sufficiently able to reproduce the safety analyses of the Applicant and perform my own analyses when necessary.

8.3.2. Categorization of Adverse Events

For 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 e 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

Other significant AEs known with LCM were also considered as listed below (Table 6).

Table 6 List of other significant AEs of Lacosamide (MedDra Preferred Terms)

Cardiac and ECG Related Terms	Suicidality Related Terms	Additional Terms
Atrioventricular block third degree	Completed suicide	Loss of consciousness
Atrioventricular block second degree	Depression suicidal	Syncope
Bradyarrhythmia	Suicidal behavior	Appetite disorder
Bradycardia	Suicidal ideation	Decreased appetite
Cardiac pacemaker insertion	Suicide attempt	Diet refusal
Atrial fibrillation	Intentional self-injury	Hypophagia
Atrial flutter	Self-injurious behavior	Food aversion
Sinus bradycardia	Self-injurious ideation	Abnormal behavior
Ventricular tachycardia	Intentional overdose	
Ventricular fibrillation	Multiple drug overdose	

Heart rate decreased Sick sinus syndrome Atrial Conduction time prolongation Atrioventricular dissociation Conduction disorder Cardiac fibrillation Cardiac flutter Sinus arrest Torsade de pointes Ventricular asystole Ventricular flutter Ventricular tachyarrhythmia Implantable defibrillator insertion	intentional Poisoning deliberate	

8.4. Safety Results

8.4.1. Deaths

There were no deaths during the study.

8.4.2. Serious Adverse Events

There were no treatment-emergent serious adverse events (SAEs) reported during the study. There was one patient who reported an SAE of gastroenteritis prior to treatment during the baseline/screening period.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were no TEAEs that resulted in discontinuation from the study. There was a patient who reported an AE of sinus bradycardia that resulted in screen failure, hence leading to study discontinuation.

8.4.4. Significant Adverse Events

There were no severe TEAES during the study.
There was one patient who had a severe AE of sleep apnea that was reported during the baseline/screening period.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

There were 7 TEAEs reported in 5 patients during the study.

Of these, the TEAEs were blood triglycerides increased (2), respiratory tract infection (2), blood cholesterol increased (1), functional gastrointestinal disorder (1), and pyrexia (1).

Reviewer's comment: There were no common TEAEs reported during the study. However, for all except 4 patients this was a single-day study, and patients received one or two doses of IV LCM. Therefore, expected TEAES in this type of study design would most likely be those uniquely related to the infusion of the drug. Given the bioequivalence of the oral and intravenous formulations, the expected TEAEs of repeated dosing of IV LCM would be expected to be similar to the common TEAEs seen in both the adult and pediatric controlled studies with oral LCM. There is no expectation that due to the lack of TEAEs identified in this open-label study that the intravenous formulation is in any way safer or with less adverse drug reactions than the oral formulation.

8.4.6. Laboratory Findings

Overall there were no consistent or clinically relevant treatment-related changes in mean or median hematology or clinical chemistry values. Low number of patients reported shifts from normal at baseline to low or high abnormal chemistry or hematology values.
As noted above, there were TEAEs reported for the abnormal clinical laboratory values of blood triglycerides increased (2 patients) and blood cholesterol increased (1 patient). The blood cholesterol increased and one of the reports of increased triglycerides were in the same patient. The events were not serious or severe, and did not lead to discontinuation from the study.

8.4.7. Vital Signs

There were no clinically relevant changes from baseline in vital signs that were consistently observed. There were some variable changes in blood pressure and heart rate noted at the visits that extended beyond a 2nd day of the study, but those results must be interpreted with caution because it included only 5 patients.

There were no vital signs-related TEAEs reported. A single patient reported a drop in heart rate of ≥ 10 bpm, with a drop from 63 to 53 bpm at 10 minutes after the infusion. This occurred in a 10-year-old boy who received a 30 minute infusion, and his heart rate had recovered by 20 minutes after the infusion back to his baseline.
A few patients reported markedly high or low diastolic blood pressures, none of which appeared clinically significant. One patient (12-year-old girl who received an infusion over 34 minutes) had a drop of > 20 mmHg in systolic blood pressure at 60 minutes post-infusion, but did not have a matching drop in DBP, and recovered at 2 hours post-infusion.

Reviewer's comment: There were no safety signals identified in review of the vital signs post-infusion. Specifically, there was no evidence that young children are more at risk for fluctuations in vital signs, including bradycardia, during or immediately post-infusion.

8.4.8. Electrocardiograms (ECGs)

Mean changes from baseline to Visit 2 and Final visit were small and similar between the two age cohorts for PR interval, QRS duration, QTcF, and QTcB. The treatment-emergent abnormal ECG findings were reviewed. There were low numbers in general of patients with treatment-emergent abnormal ECGs, with no trends between the two age cohorts. None of the treatment-emergent ECG abnormalities were clinically significant, and there were no reported ECG-related TEAEs.

Reviewer's comment: There were no new safety signals identified in this open-label study. However, LCM is known to prolong the PR interval and increase the risk for cardiac conduction changes. Given the current study design with most patients receiving only 1-2 doses, there is no reason to think that the intravenous formulation is any safer than the oral formulation in that regard. However, there did not seem to be any increased risk with administering IV LCM to pediatric patients.

8.5. Analysis of Submission-Specific Safety Issues

There were no patients who reported any of the pre-defined significant TEAEs as noted above in Table 6.

8.6. Safety Analyses by Demographic Subgroups

Given the open-label nature of the study and the small number of adverse events reported, safety analyses by demographic subgroups were not completed, other than the age and cohort comparisons outlined above. Safety of IV LCM was not analyzed by intrinsic or extrinsic factors.

8.7. Safety in the Postmarket Setting

8.7.1. Safety Concerns Identified Through Postmarket Experience

Intravenous LCM has been frequently used off-label in pediatric patients since initial approval in 2008. The Applicant did a search of the UCB Global Safety database through the Data Lock point of 31 Aug 2019 for all postmarketing case reports associated with the use of intravenous LCM in pediatric patients < 17 years. The Applicant identified 67 postmarketing cases in patients ≥ 4 to < 17 years of age, and 14 cases in patients < 4 years of age.

The identified cases were reviewed and analyzed for the LCM-specific safety concerns identified above. Additionally all fatal cases and cases of cardiac/ECG changes were reviewed. There were 2 deaths in the postmarketing cases which appeared related to the underlying etiology for the patient's seizures, and not to the medication.

There were 5 patients with serious cardiac-related events. These are described below, although many had limited details.

- One of the fatal cases above was noted to have a cardiac arrest at time of death, that appeared related to underlying condition of status epilepticus secondary to autoimmune encephalopathy, in a drug-induced coma, but the arrest occurred 2 days after initiation of LCM for continued status epilepticus.
- One patient in status epilepticus had QT prolongation noted on ECG, with limited details available for full review.
- One case reported a patient who received an LCM loading dose for refractory epilepsy, and had a normal baseline ECG with normal PR interval, but had bradycardia with a heart rate drop to 58 bpm as well as irregular heart rate one day after starting IV LCM. The event resolved and treatment was continued.
- One patient experienced bradycardia while being treated with LCM while comatose for a week with limited details available.
- There was a patient in refractory status epilepticus s/p ingestion of multiple cold medications and ibuprofen, and was comatose on concomitant lamotrigine, lorazepam, famotidine, saline, sodium acetate, and experienced 30 minute asystole directly after receiving first dose of LCM (dose and infusion duration information not available). The asystole resolved with epinephrine, but the coma and seizures remained.

Reviewer's comment: These cardiac cases outlined above may be drug-related cardiac events, but are similar to the events previously seen in adult patients treated with LCM and already described in the prescribing information. The most concerning event of asystole directly following an initial dose of LCM (dose unknown) may have been related to the intravenous administration, but unfortunately the dose and rate of infusion were not known. However, that patient may have been receiving other medications that affect cardiac conduction which would have put them at higher risk. No new safety signals were identified.

The most frequently reported preferred terms (PTs) reported in the postmarketing case reports were "no adverse event" or "ineffectiveness", with additional reports in multiple patients for seizure, sedation, and bradycardia. The common PTs reported were similar to the known LCM safety profile (bradycardia, somnolence, vertigo, fatigue, ataxia, nausea). There were no events related to syncope, falls, infusion site reactions, suicidality-related events, overdose, hepatotoxicity.

There was a single patient who reported an event concerning for DRESS, but did not meet the DRESS criteria. There were also one patient each with elevations in liver transaminases and ammonia, but both of these patients were on concomitant valproate.

Only one patient in the postmarketing database documented an infusion duration as low as 15 minutes with no cardiac concerns. This patient did develop a rash after a few infusions that was nonserious.

There were a limited number of published literature studies using the search criteria, including a total of 6 publications reporting 5 studies of intravenous LCM in pediatric patients that were reviewed for this submission, primarily for the off-label treatment of status epilepticus. The most commonly reported AE was bradycardia. No new safety concerns were identified.

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.

8.7.2. Expectations on Safety in the Postmarket Setting

The postmarket use of intravenous LCM is expected to be similar to the current off-label use, although some prescribers may be more comfortable using it in the pediatric population once it had the approved indication, so overall use may become more frequent.
Routine pharmacovigilance is recommended.

8.7.3. Additional Safety Issues From Other Disciplines

None.

8.8. Integrated Assessment of Safety

A single, open-label study of 103 patients age 1 month to < 17 years of age found no safety signals that were unique to intravenous infusion of LCM in pediatric patients when administered over 30-60 minutes. The safety profile of intravenous LCM is felt to be similar in pediatric patients to that of adult patients, and the adverse reaction profile is expected to be similar to the oral formulation given their bioequivalence.
There were no patients who received the infusion over 15 minutes, and only 4 patients received the infusion in times less than 30 minutes (21-28 minutes). Thus, there is insufficient data to determine the safety of shorter duration infusion times (< 20 minutes).

9. Labeling Recommendations

9.1. Prescription Drug Labeling

The label 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 study is intended to partially fulfill PREA PMR 2774-1 and to completely fulfill PREA PMR 3293-2 as outlined above in Table 2. The remainder of PREA PMR 2774-1 and outstanding PREA PMR 3293-1 will be addressed by a future supplement.

12. Appendices

12.1. References

See footnotes throughout.

12.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): EP0060 is not a covered study (N/A)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 136		
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): **1**		
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: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S 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)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EMILY R FREILICH
11/16/2020 10:40:14 AM

PHILIP H SHERIDAN
11/16/2020 10:42:49 AM