CLINICAL REVIEW

Application Type	NDA
Application Number(s)	218879
Priority or Standard	Standard
Submit Date(s)	March 4, 2024
Received Date(s)	March 4, 2024
PDUFA Goal Date	January 2, 2025
Division/Office	DN2/ON/OND/CDER
Reviewer Name(s)	Kevan VanLandingham, MD, PhD Philip Sheridan, MD
Review Completion Date	December 20, 2024
Established/Proper Name	lamotrigine
(Proposed) Trade Name	Subvenite
Applicant	OWP Pharmaceuticals, Inc.
Dosage Form(s)	Oral suspension, 10 mg/mL
Applicant Proposed Dosing Regimen(s)	Dosing is based on concomitant medications, indication, and patient age (see section 7.1.4 Dose and Dose-Response, below)
Applicant Proposed Indication(s)/Population(s)	**Epilepsy:** SUBVENITE® is indicated as adjunctive therapy for the following seizure types in patients aged 2 years and older: • partial-onset seizures. • primary generalized tonic-clonic (PGTC) seizures. • generalized seizures of Lennox-Gastaut syndrome. SUBVENITE® is indicated for conversion to monotherapy in adults (aged 16 years and older) with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single antiepileptic drug (AED). **Bipolar Disorder:** SUBVENITE® is indicated for the maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Not applicable, as Complete Response issued to Applicant.

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Glossary

AC	advisory committee
AE	adverse event
AED	antiepileptic drug
ANDA	abbreviated New Drug Application
AR	adverse reaction
ASM	antiseizure medication
AUC	area under the curve
BID	twice daily
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BRV	brivaracetam
CBER	Center for Biologics Evaluation and Research
CBN	cenobamate
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
Cmax	maximum concentration
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
DMF	Drug Master File
DPMH	Division of Pediatric and Maternal Health
DRESS	drug reaction with eosinophilia and systemic symptoms
ECG	electrocardiogram
eCTD	electronic common technical document
ESL	eslicarbazepine
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GBP	gabapentin
GCP	good clinical practice

GRMP	good review management practice
GSK	GlaxoSmithKline
ICH	International Council for Harmonization
IND	Investigational New Drug Application
iPSP	initial Pediatric Study Plan
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
LCM	lacosamide
LD	listed drug
LEV	levetiracetam
LTG	lamotrigine
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MSF	median seizure frequency
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OS	oral suspension
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OXC	oxcarbazepine
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PeRC	Pediatric Review Committee
PGTC	primary generalized tonic-clonic
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PO	per os (by mouth)
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
QD	daily
QTcB	QT interval corrected with Bazett formula
REMS	risk evaluation and mitigation strategy
RPCT	randomized, placebo-controlled trial

SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SJS	Stevens Johnson Syndrome
SOC	standard of care
TEAE	treatment emergent adverse event
TEN	toxic epidermal necrolysis
TGB	tiagabine
TID	three times daily
TPM	topiramate
VPA	valproic acid

1. Executive Summary

1.1. Product Introduction

Lamotrigine is a phenyltriazine class antiseizure medication (ASM). The lamotrigine NDA 020241 was first approved by FDA on December 27, 1994.

The Listed Drug (LD) which supports this NDA is Lamictal NDA 020241 (lamotrigine), 100 mg tablet, to demonstrate efficacy and safety. Lamictal was initially synthesized by chemists at Burroughs-Wellcome, and subsequently marketed by Glaxo-Wellcome and later GlaxoSmithKline (GSK).

OWP Pharmaceuticals, Inc. (the Applicant) is seeking FDA approval for lamotrigine oral suspension, 10 mg/mL,

1. as adjunctive therapy for the following seizure types in patients aged 2 years and older:
   - partial-onset seizures.
   - primary generalized tonic-clonic (PGTC) seizures.
   - generalized seizures of Lennox-Gastaut syndrome.
2. for conversion to monotherapy in adults (aged 16 years and older) with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single antiepileptic drug (AED).
3. for the maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy.

The initial dosing regimen for lamotrigine tablets is complicated, due to the increased risk of allergic reactions and other adverse events. There is a prolonged up-titration, that is defined according to the concomitant medications (which may inhibit or induce the metabolism of lamotrigine), indication, and patient age. Lamotrigine dose escalation tables, dependent upon concomitant medications, indication and patient age allow for a consistent initiation of therapy during initiation of treatment with lamotrigine tablets.

The proposed product in NDA 218879 is lamotrigine oral suspension, 10 mg/mL, supplied as (b) (4) mL in an 8-ounce ((b) (4) mL) bottle. The product will be administered either with an appropriate syringe or a graduated medicine cup, according to the established dosing guidelines for Lamictal.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The evidence of effectiveness for lamotrigine in the treatment of focal seizures, generalized tonic-clonic seizures and seizures associated with Lennox-Gastaut Syndrome, and for the maintenance treatment of bipolar I disorder is based upon the Applicants in-vitro bioequivalence

and bioavailability study to the LD, Lamictal (lamotrigine), NDA 020241. The effectiveness of lamotrigine in both epilepsy and bipolar disorder has been the subject of recent Cochrane and other reviews (Panebianco, 2023; Campos, 2018), Zhang, 2021, Hashimoto, 2021).

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Subvenite (lamotrigine oral suspension, 10 mg/ml) is a new formulation of an already approved drug (lamotrigine). Subvenite is proposed for the same indications as the listed drug (LD), Lamictal (lamotrigine) tablets, NDA 020241:

1. as adjunctive therapy for the following seizure types in patients aged 2 years and older:
   - partial-onset seizures.
   - primary generalized tonic-clonic (PGTC) seizures.
   - generalized seizures of Lennox-Gastaut syndrome.
2. for conversion to monotherapy in adults (aged 16 years and older) with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single antiepileptic drug (AED).
3. for the maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy.

This submission is a 505(b)(2) application using Lamictal (lamotrigine) tablets, approved under NDA 020241, as the LD. The determination of benefit and risk for this new formulation of lamotrigine depends on the previous findings of effectiveness and safety for the LD and on a demonstration of adequate bridging with bioavailability and bioequivalence studies from Subvenite to the LD.

Lamotrigine is currently marketed as immediate release tablets, extended-release tablets, orally disintegrating tablets, and tablets for suspension.

Lamotrigine has a well characterized safety profile. The primary risk associated with lamotrigine use is that of severe allergic reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and multiorgan hypersensitivity reactions (drug reaction with eosinophilia and systemic symptoms, DRESS). Additional risks include hemophagocytic lymphohistiocytosis, cardiac rhythm and conduction abnormalities, blood dyscrasias, aseptic meningitis, suicidal behavior and ideation, and medication errors. Common adverse reactions with lamotrigine use include dizziness, headache, diplopia, ataxia, nausea, vomiting, abdominal pain, blurred vision, and somnolence. Despite these risks and adverse reactions, lamotrigine has proven to be an effective medication for the treatment of epilepsy and bipolar disorder.

Subvenite has been shown to have comparative bioavailability to the LD, Lamictal, in a pivotal comparative bioavailability study and a food effect study in healthy adult volunteers. No new or unexpected adverse events were discovered in the course of the development program of Subvenite in healthy adult volunteers.

However, because the Office of Product Quality (OPQ) review team found that the Applicant failed to characterize adequately the identity, strength, and purity of the proposed drug product (discussed in Section 3 of this review), this NDA will receive a Complete Response.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Approximately 0.5 to 1% of the US population suffers from epilepsy, a condition of recurrent seizures, most commonly focal seizures, but also generalized seizures. • Approximately 30% of patients continue to have seizures, despite treatment with multiple antiseizure medications (ASMs). • Patients with uncontrolled seizures are at risk of increased morbidity and mortality. • Epilepsy can begin at any time of life, but it is most commonly first diagnosed in children, and people over the age of 65. • Bipolar disorder is characterized by alternating episodes of depression and either mania (Bipolar I) or hypomania (Bipolar II). • The prevalence of bipolar disorder I and II in the US is estimated to be approximately 4%. • Bipolar disorder is most often identified in young adults, but it can occur in adolescents. It is rare but can be diagnosed in children. • The presence of severe manic episodes, potential psychotic features, and a propensity for cycling between manic and depressive episodes contribute to higher functional impairment and a higher risk of hospitalization in patients with bipolar I.	Epilepsy and bipolar disorder are serious diseases with significant morbidity and mortality which are often refractory to therapy, and which may require multiple effective treatments with formulations suitable for children and adults.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• More than 20 ASMs have been approved for the treatment of focal or generalized seizures. • The most common types of medications prescribed for bipolar disorder include mood stabilizers and atypical antipsychotics. Mood stabilizers such as lithium, lamotrigine, and valproate can help prevent mood episodes or reduce their severity. Lithium also can decrease the risk of suicide. • Lamotrigine is currently marketed as immediate release tablets, extended-release tablets, tablets for oral suspension and fast melt tablets. Currently, there is no marketed premixed oral suspension or solution formulation of lamotrigine.	Lamotrigine is approved and commonly used for the treatment of epilepsy and bipolar disorder. There is a need for a premixed oral solution or suspension of lamotrigine for individuals who have difficulty administering or receiving the currently marketed formulations of lamotrigine.
Benefit	• Lamotrigine has been previously demonstrated to improve seizure control in multiple seizure types and to delay the time to occurrence of manic episodes when used as a maintenance therapy of bipolar disorder. • Subvenite (lamotrigine oral suspension) has been shown to have comparative bioavailability to the LD, Lamictal, in a pivotal comparative bioavailability study and a food effect study in healthy adult volunteers. • This new oral suspension formulation (Subvenite) will facilitate lamotrigine use in very young patients, in patients who have difficulty swallowing the currently marketed oral formulations of lamotrigine, and in patients requiring administration of lamotrigine by gastric or gastrojejunal tube	Subvenite will provide another option to patients who have difficulty receiving the currently marketed formulations of lamotrigine including children, elderly patients, and patents requiring a gastric or gastrojejunal tube.
Risk and Risk Management	• The serious risks for lamotrigine include: ○ Allergic reactions, including Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) ○ Drug-drug interactions affecting lamotrigine metabolism and	The adverse effects and drug-drug interactions of Subvenite are the same as those of the LD Lamictal and can be managed by the proposed extensive labeling instructions and Medication Guide which align with that of the LD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	effects of lamotrigine on other drugs (e.g. estradiol) ○ Potential cardiac rhythm and conduction abnormalities • These adverse events have been adequately managed by the extensive instructions in current approved labeling and the Medication Guide of the LD, Lamictal. • No new or unexpected adverse events were identified in the development program of this new formulation of lamotrigine. •	Due to the deficiencies in product quality, a Complete Response action will be taken for this application, therefore, labeling recommendations will not be made, and postmarketing requirements (PMRs) will not be issued during this review cycle.

1.4. Patient Experience Data

No patient experience data was provided with this application. Review articles summarizing clinical data on the use of lamotrigine in the treatment of epilepsy and the treatment of bipolar disorder are listed in the References below.

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

			Section where discussed, if applicable
☐	The patient experience data that was submitted as part of the application include:		
	☐	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.)	Section 1.2. Conclusions on the Substantial Evidence of Effectiveness
	☐	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)	

2. Therapeutic Context

2.1. Analysis of Condition

Uncontrolled epilepsy is a common disorder with increased morbidity and mortality. This oral suspension formulation will allow for dosing in epilepsy patients who are very young or who have difficulty swallowing pills.

2.2. Analysis of Current Treatment Options

Table 1 Summary of drugs currently approved for treatment of partial onset seizures[1]

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.
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

[1] https://www.epilepsy.com/tools-resources/seizure-medication-list (Accessed December 12, 2024.

Product (s) Name	Relevant Pediatric Indication	Year of Pediatric Approval	Route and Frequency of Admin.	Efficacy Information	Important Safety and Tolerability Issues
Lacosamide (LCM)	Treatment of partial-onset seizures in patients 4 years of age and older	2017	PO only (safety of IV formulation unknown in pediatric patients), 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,
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
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,

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
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
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
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
Cenobamate (CBN)	Treatment of partial-onset seizures in adult patients		PO, QD	2 RCTs with primary endpoint of median reduction in seizure frequency in adults with POS, comparing baseline vs placebo, with statistically significant difference.	DRESS, QT shortening, somnolence and fatigue, dizziness and disturbance in gait and coordination, cognitive dysfunction, visual changes.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

This 505(b)(2) application relies on the FDA's findings of safety and effectiveness for the LD, Lamictal, NDA 020241, which was initially approved in 1994.

3.2. Summary of Presubmission/Submission Regulatory Activity

Date	Key Regulatory History
8/16/2018	Type B pre-IND meeting Written Responses – 505(b)(2) application appears appropriate. New dosage form triggers PREA and iPSP. Sponsor plans to conduct BE study, using Lamictal 100 mg tablets as the Listed Drug, and NDA will rely on LD safety and efficacy. No additional Nonclinical studies are required. CMC guidance provided.
2/13/2019	Sponsor submitted new IND 140073.
4/4/2019	IND was placed on a Full Clinical Hold - Sponsor had not provided adequate CMC information to support the safety of the proposed study.
6/3/2019	Remove Full Clinical Hold
9/21/2021	iPSP submitted
11/29/2021	Proprietary name granted
12/20/2021	Written Response to iPSP; required edits to be submitted within 90 days.
3/17/2022	Incomplete Response to required iPSP edits
9/29/2022	Email to Sponsor to notify PREA required study 1 month to 2 years if NDA approved.
10/4/2023	Type B Meeting Request denied, due to request being substantially incomplete.
12/4/2023	Type B Pre-NDA Meeting Written Responses, with one CMC question/response
3/12/2024	Proprietary name acknowledged
3/24/2024	NDA (b) (4) filed by Applicant
6/4/2024	Proprietary name granted
7/9/2024	Sponsor resubmitted previous non agreed iPSP
8/8/2024	Initial No Agreement Letter iPSP
11/7/2024	8-week Post marketing Requirement Communication Letter

3.3. Foreign Regulatory Actions and Marketing History

Lamotrigine oral suspension, 10 mg/mL has had no known foreign submissions, and it is not marketed inside or outside of the US.

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

4.1. Office of Scientific Investigations (OSI)

The Office of Study Integrity and Surveillance (OSIS) determined that inspections were not needed for Actimus Biosciences, Pvt. Ltd., (Varun Towers) Visakhapatnam, as it was inspected in January 2024 for ANDAs 218783 and 077440/S-005, and (b) (4) , as it was inspected remotely in (b) (4) for ANDAs NON-RESPONSIVE NON-RESPONSIVE . Data from the reviewed studies were determined to be reliable.

4.2. Product Quality

The OPQ review team determined that the proposed drug substance, microbiology, and labeling were adequate.

However, the OPQ review team found that the Applicant had not provided adequate information on the proposed drug product to ensure its identity, strength, and purity. The outstanding deficiencies are related to inadequate information to support acceptable quality control of the drug product. The reviewers note that "extensive deficiencies related to the proposed dissolution method, validation of analytical methods used for release and stability testing, lack of in-use stability data, and control of container closure leachables were communicated as information requests (IRs) early in the review cycle. The Applicant adequately addressed some of the IRs; however, the responses to the remaining IRs are either incomplete (i.e., 'reports to be submitted at a later time') or inadequate."

In addition, the OPQ team was advised by the Office of Regulatory Affairs that the manufacturing inspection made a (b) (4) recommendation for one of the drug substance manufacturing facilities (b) (4).

See the complete response letter for the OPQ team's detailed comments to the Applicant regarding these deficiencies and the actions required to address them.

The OPQ review team recommends a Complete Response for NDA 218879 Subvenite.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

Not applicable. Nonclinical findings supported by LD, Lamictal NDA 020241.

4.5. Clinical Pharmacology

Two Phase 1 Clinical Pharmacology studies were conducted with healthy adult volunteers.

The first bioequivalence study was LAMO-159-22 (Original study number was changed from 018/19 to LAMO-159-22), entitled, An open label, randomized, balanced, single-dose, two-sequence, two-treatment, two-period, two-way crossover, oral bioequivalence study of Lamotrigine oral suspension 10 mg/mL with LAMICTAL (lamotrigine) tablets 100 mg, in normal healthy adult human subjects under fasting conditions.

The Table below displays the confidence intervals and final variance parameters for ration (Test/Reference) for lamotrigine OS, 10 mg/mL vs Lamictal 100 mg tabs (N=34):

Table 2: Ratio of the least squares geometric means of pharmacokinetic parameters and 90% confidence intervals of lamotrigine OS, 10 mg/mL versus Lamictal, 100 mg tablets.

Parameters	Geometric Mean		% Ratio	90% CI		Power	ISCV %
	Test	Reference	T/R	Lower	Upper		
Ln (C_{max}) (ng/mL)	1856.5930	1733.1991	107.12	100.07	114.67	99.93	16.6
Ln (AUC_{0-t}) (hr*ng/mL)	73266.7508	72609.0111	100.91	98.06	103.83	>99.99	6.9
Ln (AUC_{0-inf}) (hr*ng/mL)	79522.2104	78732.3721	101.00	97.82	104.30	>99.99	7.8

Source: Clinical Study Report-Protocol LAMO-159-22, Table 2 on page 22 of 112.

An independent review of the data by FDA Clinical Pharmacology Reviewer Dawei Lee:

Table 3: Ratio of the Least Squares Geometric Means of PK parameters and 90% Confidence Intervals of Lamotrigine (n=34, Reviewer's Analysis)

Comparison (Test vs Reference)	Parameter	Test Geometric LSM	Reference Geometric LSM	Test/ Reference (%)	90% Confidence Interval
Subvenite lamotrigine oral suspension vs LAMICTAL lamotrigine tablet	Cmax (ng/mL)	1857.08	1731.47	107.26	100.36-114.63
	AUC0-t (hr*ng/mL)	73248.36	72551.76	100.96	98.23-103.76
	AUC0-inf (hr*ng/mL)	79497.91	78666.12	101.06	97.98-104.23

Source: Clinical Pharmacology Reviewer's independent analysis.

Thus, these data reveal that under fasting conditions, lamotrigine OS, 10 mg/mL meets the acceptable limits of 80.0% to 125% required to demonstrate bioequivalence with Lamictal 100 mg tablets.

The second study was LAMO-160-22, entitled: An open label, balanced, randomized, single

dose, two treatment, three treatment condition, three period, six sequence, crossover, oral food effect and fed comparative bioavailability and bioequivalence study of Lamotrigine oral suspension 10 mg/mL with LAMICTAL (lamotrigine) tablets 100 mg, in normal healthy adult human subjects.

For the Fasted and Fed components of LAMO-160-22, the Applicant reported the following findings in Table # and #:

Table 4: Geometric means and confidence intervals of test (fasting) versus test (fed) for lamotrigine OS, 10 mg/mL (N=33).

Parameters	Geometric Mean		% Ratio	90% CI		Power	ISCV %
	Test	Reference		Lower	Upper		
Ln (C_{max}) (ng/mL)	1730.4904	1419.0990	121.94	111.81	132.99	98.64	21.0
Ln (AUC_{0-t}) (hr*ng/mL)	64746.8285	65832.9591	98.35	92.81	104.22	>99.99	13.9
Ln (AUC_{0-inf}) (hr*ng/mL)	67863.3328	68764.2653	98.69	93.03	104.69	99.99	14.2

Source: Clinical Study Report-Protocol LAMO-160-22, Table 2A on page 23 of 132.

Table 5: Geometric means and confidence intervals of test, lamotrigine OS 10 mg/mL (fed) versus reference, Lamictal, 100 mg tablets (fed) for lamotrigine (N=33)

Parameters	Geometric Mean		% Ratio	90% CI		Power	ISCV %
	Test	Reference		Lower	Upper		
Ln (C_{max}) (ng/mL)	1427.2503	1396.0317	102.24	96.69	108.10	>99.99	13.3
Ln (AUC_{0-t}) (hr*ng/mL)	65994.5244	61333.0320	107.60	102.25	113.23	>99.99	12.2
Ln (AUC_{0-inf}) (hr*ng/mL)	68963.0683	64845.2172	106.35	100.83	112.17	>99.99	12.7

Source: Clinical Study Report-Protocol LAMO-160-22, Table 2B on page 24 of 132.

An independent review of the data by FDA Clinical Pharmacology Reviewer Dawei Lee:

Table 6: Geometric Means and Confidence Intervals of Test (Fasting) versus Test (Fed) for Lamotrigine OS, 10 mg/mL (N = 33, Reviewer's Analysis)

Comparison	Parameter	Test Geometric LSM	Reference Geometric LSM	Test/ Reference (%)	90% Confidence Interval
	Cmax (ng/mL)	1737.08	1419.62	122.36	111.88-133.82

Subvenite lamotrigine oral suspension (Fasting vs Fed)	AUC0-t (hr*ng/mL)	63938.37	64954.04	98.44	93.20-103.97
	AUC0-inf (hr*ng/mL)	66841.92	67683.17	98.76	93.46-104.35

Source: Clinical Pharmacology Reviewer's independent analysis.

Thus, these data reveal that there is slight food effect on the clinical pharmacology of lamotrigine OS, 10 mg/mL, demonstrating that high fat food slightly decreased the Cmax of lamotrigine and had no impact on the AUCs of lamotrigine.

Clinical Pharmacology Recommendation: The Applicant established an adequate PK bridge between Subvenite lamotrigine OS, 10 mg/mL and the LD (LAMICTAL lamotrigine 100 mg tablet), allowing the applicant to rely upon FDA's previous findings of LD for efficacy and safety.

4.6. Devices and Companion Diagnostic Issues

Not applicable

4.7. Division of Pediatric and Maternal Health

The Division of Pediatric and Maternal Health (DPMH) was consulted, to provide input into Labelling Review, PREA, potential PMRs, and PeRC Preparation Assistance and Meeting Attendance. DPMH input was provided as requested.

4.8. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 7: Listing of Clinical Trials Relevant to this NDA/BLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)					
LAMO-159-22	N/A	An open label, randomized, balanced, single-dose, two-sequence, two-treatment, two-period, two-way crossover, oral bioequivalence study of lamotrigine oral suspension 10 mg/mL with LAMICTAL (lamotrigine) tablets 100 mg in adult healthy volunteers (HVTs) under fasting conditions.	Test: Lamotrigine Oral Suspension 10 mg/mL, 100 mg, administered orally Reference: LAMICTAL (lamotrigine) tablets 100 mg administered	Bioequivalence	Single dose X two	Enrolled: 36 subjects Completed: 34 subjects	Healthy male and female adult, human subjects.
LAMO-160-22-	N/A	An open label, balanced, randomized, single dose, two treatment, three treatment condition, three period, six sequence, crossover, oral food effect and fed comparative bioavailability and bioequivalence study of Lamotrigine oral suspension 10 mg/mL Inc. with LAMICTAL (LAMOTRIGINE) TABLETS 100 mg, in HVTs.	Test: Lamotrigine Oral Suspension 10 mg/mL, 100 mg, administered orally Reference: LAMICTAL (lamotrigine) tablets 100 mg administered	Bioequivalence	Single dose X two	Enrolled: 36 subjects Completed: 33 subjects	Healthy male and female adult, human subjects.

5.2. Review Strategy

As the Applicant demonstrated bioequivalence to the LD, the majority of the safety and all of the efficacy assessments are attributed to the LD. The review of the limited safety data from the two Bioequivalent studies will be summarized below.

6. Review of Relevant Individual Trials Used to Support Efficacy

No trials were conducted to support efficacy. The demonstration of substantial evidence of efficacy of lamotrigine is based upon the prior approval of Lamictal (LD) NDA 020241, which the Applicant was able to bridge to via the bioequivalence studies.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Based upon the bioequivalence of lamotrigine oral suspension with the LD, Lamictal, the proposed product is being submitted via a 505(b)(2) pathway, relying on the findings of efficacy and safety of the LD. Dosing of lamotrigine is based on concomitant medications, indication, and patient age, as presented in the tables from below (Lamictal US Label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020241s064,020764s057,022251s028lbl.pdf).

7.2. Integrated Assessment of Effectiveness

As the reference product, Lamictal as LD, and the proposed product are bioequivalent, the proposed drug product, lamotrigine oral suspension, 10 mg/mL, is deemed adequately bridged to the efficacy data of the listed drug per 21 CFR 320.24(a)(1).

8. Review of Safety

8.1. Safety Review Approach

Based upon the bioequivalence of lamotrigine oral suspension with the LD, Lamictal, the proposed product is being submitted via a 505(b)(2) pathway, relying on the previous findings of safety. From the two Clinical Pharmacology studies conducted for this NDA, dosing of lamotrigine was limited to one or two doses.

Study LAMO-159-22 was an open label, randomized, balanced, single-dose, two-sequence, two-

treatment, two-period, two-way crossover, oral bioequivalence study of Lamotrigine oral suspension 10 mg/mL with LAMICTAL (lamotrigine) tablets 100 mg, in normal healthy adult human subjects under fasting conditions. Baseline and regular vital signs and ECG were obtained during the study. Laboratory tests, including hematology, chemistry, urinalysis and urine drug screen, were performed during the study.

Study LAMO-160-22 was an open label, balanced, randomized, single dose, two treatment, three treatment condition, three period, six sequence, crossover, oral food effect and fed comparative bioavailability and bioequivalence study of Lamotrigine oral suspension 10 mg/mL with LAMICTAL (lamotrigine) tablets 100 mg, in normal healthy adult human subjects. Baseline and regular vital signs and ECG were obtained during the study. Baseline and regular laboratory tests were performed during the study, including hematology, chemistry, urinalysis and urine drug screen.

8.2. Review of the Safety Database

The determination of safety of Subvenite (lamotrigine OS, 10 mg/mL) relies upon the finding of safety of the LD, Lamictal 100 mg tablets. The primary limitation of the safety data included in this NDA is that there were no placebo controls for comparison; therefore, the primary assessment of safety remains dependent on data from the placebo-controlled trials of the LD.

8.2.1. Overall Exposure

In Study LAMO-159-22, 36 subjects were enrolled, and 35 subjects received at least one dose of either the reference treatment (Lamictal, 100 mg tablet) or test treatment (lamotrigine OS, 100 mg). Two subjects withdrew from the study for personal reasons, with 1 subject (b) (6) withdrawing during predose vital signs, and the other subject withdrawing 24 hours after the dose of the first study drug, reference treatment, as detailed below in Section 8.4.3. A total of 34 completed the study.

In Study LAMO-160=22, 36 subjects were enrolled in the study and all 36 received at least 1 dose of study drug. A total of 33 subjects completed the study, with 3 subjects withdrawing from the study due to adverse events, as detailed below in Section 8.4.3

8.2.2. Relevant characteristics of the safety population:

Limited demographic information was collected on each subject, including sex, age weight and BMI. Other demographic information, such as race, was not collected in these studies.

Table 8: Demographic characteristics, subjects of Study LAMO-159-22

Demographic characteristic	**Total N= 35 (n %)**
Sex	
Male	33 (91.7)
Female	3 (8.3)
Age (years)	
Mean	33.8
Median	35.5
Min, max	22, 43
Weight (kg)	
Mean	63.5
Median	63.6
Min, Max	51.0, 83.8
Body Mass Index	
Mean	23.0
Median	24.2
Min, Max	18.7,24.8

Table 9: Demographic characteristics, subjects of Study LAMO-160-22

Demographic characteristic	**Total N= 36 (n %)**
Sex	
Male	32 (88.9)
Female	4 (11.1)
Age (years)	
Mean	32.3
Median	32.0
Min, max	22, 43
Weight (kg)	
Mean	63.7
Median	63.1
Min, Max	51.8, 75.9
Body Mass Index	
Mean	23.2
Median	24.1
Min, Max	18.9,24.9

8.2.3. Adequacy of the safety database:

The safety database provides limited safety data from 1 or 2 doses of lamotrigine in healthy adult volunteers. No new safety issues were identified. The primary assessment of safety remains dependent upon the data from placebo-controlled trials of the LD, Lamictal.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

See the discussion in Section **Error! Reference source not found.** regarding OSIS assessment, which from prior inspections of these study sites, the data from the reviewed studies were determined to be reliable.

8.3.2. Categorization of Adverse Events

In protocols LAMO-159-22 and LAMO-160-22, an adverse event (AE) was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal product, whether considered related to the medicinal product or not. This could include any unfavorable and unintended signs (such as rash or enlarged liver), or symptoms (such as nausea or chest pain), an abnormal laboratory finding (including blood tests) or a disease temporarily associated with the use of the study medication.

The severity of the adverse events was graded as follows:

Grade 1: Mild; Transient or mild discomfort; no limitation in activities of daily living; no medical intervention/ therapy required.

Grade 2: Moderate; Mild to moderate limitation in activities of daily living; some assistance may be needed; no or minimal medical intervention/therapy required.

Grade 3: Severe; Marked limitation in activities of daily living, some assistance usually required; medical intervention/therapy required hospitalizations possible.

Grade 4: Life-threatening; Extreme limitation in activities of daily living, significant assistance required; significant medical intervention/ therapy required hospitalization probable.

Grade 5: Death; The relationship of the adverse event to the study medication will be judged by the Investigator.

A serious adverse event was defined as an untoward medical occurrence during clinical trial that was associated with death, in-patient hospitalization (in case the study was being conducted all outpatient), prolongation of hospitalization (in case the study was being conducted on inpatient), persistent or significant disability or in capacity, a congenital anomaly or birth defect or was otherwise life-threatening.

Reviewer Comment: The AE definitions and characterizations used in Study LAMO-159-22 and LAMO-160-22 are acceptable.

8.3.3. Routine Clinical Tests

The safety assessment methods and time points are acceptable, as described in Section 8.1 above and Sections 8.4.6, 8.4.7, and 8.4.8 below.

8.4. Safety Results

8.4.1. Deaths

No deaths were reported during the two Phase 1 Clinical Pharmacology studies.

8.4.2. Serious Adverse Events

No serious adverse events were reported during the two Phase 1 Clinical Pharmacology studies.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In Study LAMO-159-22, there were 2 subjects who dropped out of the study due to personal reasons. Subject (b) (6) withdrew from the study during pre-dose vital signs before any dosing, and Subject (b) (6) withdrew from the study 24 hours after dosing in period I (Lamictal 100 mg tablet).

In Study LAMO-160-22, there were 3 subjects who dropped out of the study due to adverse events (AEs).

One AE (rash) leading to withdrawal occurred in subject (b) (6), 8 hours post dose sample in period I (Lamictal tablet, 100 mg, fasting), cohort II, and it was considered to have moderate intensity. The rash was not noted to involve mucosal surfaces. The subject received a 100 mg injection of hydrocortisone and a 22.75 mg injection of pheniramine. The rash was resolved after 2 hours, and the subject was withdrawn from the study.

Two AEs leading to withdrawal, one of nausea and vomiting in subject (b) (6), 0.67 hours post dose sample in period II (lamotrigine oral suspension, 100 mg), cohort I. and Subject (b) (6) was treated with ondansetron 4 mg IV for the nausea and vomiting of mild intensity, with resolution of the nausea and vomiting after approximately 45 minutes. Subject (b) (6) experienced an adverse event of fever of mild intensity 24 hours post dose sample in period I (Lamictal tablet, 100 mg, fasting), cohort II. Subject (b) (6) was treated with acetaminophen orally 625 mg X 2, with resolution of the fever after 9.25 hours. Both AEs resolved prior to the subjects exiting the study.

8.4.4. Significant Adverse Events

No additional significant adverse events occurred during these trials.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

In Study LAMO-159-22, no adverse events were reported.

In Study LAMO-160-22, a total of 3 adverse events were reported, as described above in Section 8.4.3:

8.4.6. Laboratory Findings

Laboratories assessed during both studies included complete blood counts (hemoglobin, hematocrit, white blood cell count with differential and platelets), serum chemistries (sodium, potassium, creatinine, urea, glucose, beta HCG (for women only), ALT, AST, alkaline phosphatase, bilirubin, cholesterol, albumin and total protein), urine toxicology screen (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, ethanol, and morphine), urinalysis with microscopy, and HLA 1A and 1B antigen PCR typing.

In Study LAMO-159-22, all pre and post dose laboratory assessments were within normal limits. Urine toxicology screening was negative in all subjects.

In Study LAMO-160-22, all pre and post dose laboratory assessments were within normal limits. Urine toxicology screening was negative in all subjects.

Reviewer Comment: Laboratory values were reviewed in detail, and all were within normal limits throughout both studies.

8.4.7. Vital Signs

Vital signs collected during both studies included weight, height, BMI, oral temperature, oxygen saturation, heart rate, diastolic blood pressure, and systolic blood pressure.

In Study LAMO-159-22, all pre and post dose vital signs were within normal limits.

In Study LAMO-160-22, all pre and post dose vital signs were within normal limits. Temperature was reported in degrees Fahrenheit throughout. Also, subjects (b) (6) did not report for some ambulatory post dose vital signs. Subsequent vital signs in these subjects were all within normal limits.

8.4.8. Electrocardiograms (ECGs)

In Study LAMO-159-22, 3 ECGs were to be performed on all subjects. Half of the subject's ECGs were interpreted as normal. Of the 17 abnormal subject's ECGs, 9 were abnormal due to sinus arrhythmia, 5 had early repolarization with or without sinus arrhythmia, and 3 had short PR interval. All findings were considered not clinically relevant by the Applicant.

In Study LAMO-160-22, 2 to 4 ECGs were to be performed on all subjects, and 22 subject's ECGs were read as normal. Sinus arrhythmia was noted in 8 subjects, short PR interval was noted in 4 subjects, 1 subject had short PR on 1 ECG and sinus arrhythmia on another ECG, and 1 subject had low voltage QRS. All findings were considered not clinically relevant by the Applicant.

This reviewer has considered the findings, and the reviewer is in agreement that these findings are not clinically significant, and there were no relevant changes during the studies.

8.4.9. QT

In Study LAMO-159-22, all subjects had QTcB values within normal limits at baseline, and follow-up QTcB values showed no significant shortening or prolongation after dosing.

In Study LAMO-160-22, all subjects had QTcB values within normal limits at baseline, and follow-up QTcB values showed no significant shortening or prolongation after dosing.

Reviewer Comment: QTcB values from both studies were reviewed in detail. All were within normal limits at baseline, and there were no significant shifts in values.

8.4.10. Immunogenicity

Not applicable

8.5. Analysis of Submission-Specific Safety Issues

HLA Class 1A and 1B antigen PCR were assessed on each subject, and all were negative. Additional data is reliant on the LD.

8.6. Safety Analyses by Demographic Subgroups

No demographic subgroup analyses were conducted on these healthy adult volunteers who participated in Studies LAMO-159-22 and LAMO-160-22.

8.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Data is reliant on the LD.

8.8.2. Human Reproduction and Pregnancy

Data is reliant on the LD.

8.8.3. Pediatrics and Assessment of Effects on Growth

Data is reliant on the LD.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data is reliant on the LD, Lamictal. The Lamictal Label has an overdosage Section 10, but it does not have a Section 9 (Drug Abuse and Dependence). There are no known abuse-related issues with Lamictal. There are limited reports in the literature that suggest that lamotrigine treatment may be of benefit in patients with drug abuse disorders.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable

8.9.2. Expectations on Safety in the Postmarket Setting

Lamictal has been marketed for 20 years in the US and worldwide. Pharmacovigilance of adverse events is maintained by GSK.

8.9.3. Additional Safety Issues from Other Disciplines

Not applicable.

8.10. Integrated Assessment of Safety

As the reference product, Lamictal as LD, and the proposed product are bioequivalent, the proposed drug product, lamotrigine oral suspension, 10 mg/mL, is deemed adequately bridged to the safety data of the listed drug per 21 CFR 320.24(a)(1). This review summarizes the safety data collected primarily from 67 healthy adult volunteers during 2 studies which assessed PK and safety, in a single dose of pharmacokinetic assessment. The clinical safety monitoring was appropriate and capable of identifying major safety signals. Overall, the systemic safety findings from this submission are consistent with those from the LD, Lamictal, and examination findings and AEs referable to potential local toxicity were mild.

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting was not considered necessary for this 505(b)(2) NDA

Application.

10.Labeling Recommendations

10.1. Prescription Drug Labeling

The labeling for lamotrigine oral suspension will use the existing labeling from Lamictal, with minor editorial changes.

11.Risk Evaluation and Mitigation Strategies (REMS)

A REMS was not required for this application to ensure that the product's benefits outweigh its risks in the postmarket setting.

12.Postmarketing Requirements and Commitments

As this NDA submission will receive a Complete Response, there will be no postmarketing requirements or commitments.

13. Appendices

13.1. References

Campos MSA, Ayres LR, Morelo MRS, Carizio FAM, Pereira LRL. Comparative efficacy of antiepileptic drugs for patients with generalized epileptic seizures: systematic review and network meta-analysis. Int J Clin Pharm 2018, 40(3):589-598.

Hashimoto Y, Kotake K, Watanabe N, Fujiwara T, Sakamoto S. Lamotrigine in the maintenance treatment of bipolar disorder. Cochrane Database of Systematic Reviews 2021, Issue 9. Art. No.: CD013575. DOI: 10.1002/14651858.CD013575.pub2.

Nierenberg AA, Agustini B, Kohler-Forsberg O, Cusin C, Katz D, Sylvia LG, Peters A, Berk M. Diagnosis and treatment of bipolar disorder – a review. JAMA 2023, 330(14): 1370-1380.

Panebianco M, Bresnahan R, Marson AG. Lamotrigine add-on therapy for drug-resistant focal epilepsy. Cochrane Database of Systematic Reviews 2023, Issue 12. Art. No.: CD001909. DOI: 10.1002/14651858.CD001909.pub4.

Zhang L, Wang J and Wang C. Efficacy and safety of antiseizure medication for Lennox-Gastaut syndrome: a systematic and network meta-analysis. Devel Med & Child Neurol. 2022 64(3): 305-313.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): LAMO-159-22 and LAMO-160-22

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 15		
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): 0		
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)): N/A Compensation to the investigator for conducting the study where the value could be		

influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor: Sponsor of covered study: _____		
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) _____		
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/

KEVAN E VANLANDINGHAM
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Clinical Review of NDA 218879

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