CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216185Orig1s000

SUMMARY REVIEW

Summary Review

Date	May 3, 2023
From	Philip H. Sheridan, MD Paul R. Lee, MD, PhD
Subject	Summary Review
NDA/BLA # and Supplement#	216185
Applicant	Aucta Pharmaceuticals, Inc.
Date of Submission	July 7, 2022
PDUFA Goal Date	May 7, 2023
Proprietary Name	Motpoly XR
Established or Proper Name	Lacosamide
Dosage Form(s)	Lacosamide extended-release capsules 100 mg, 150 mg, 200 mg
Applicant Proposed Indication(s)/Population(s)	Treatment of partial-onset seizures in patients 17 years of age and older
Applicant Proposed Dosing Regimen(s)	Initial dosage for monotherapy: 200 mg once daily; Initial dosage for adjunctive therapy: 100 mg once daily; Maximum dosage: (b) (4) mg once daily; (b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of partial-onset seizures in adults and in pediatric patients weighing at least 50 kg
Recommended Dosing Regimen(s) (if applicable)	See approved labeling

1. Benefit-Risk Assessment

Motpoly XR (lacosamide extended-release capsules) is a new formulation of an already approved drug substance (lacosamide). In this 505(b)(2) application, the Applicant proposes Motpoly XR for one of the indications (treatment of partial-onset seizures [POS] in patients 17 years of age and older) of the listed drug (LD), Vimpat (lacosamide immediate release).

Due to the previous approval of Vimpat (lacosamide immediate release) in 2008 for the indication of the treatment of partial onset seizures, the risks and benefits associated with lacosamide (LCM) are well known and established. The four Phase 1 pharmacokinetic (PK) studies conducted to establish the pharmacokinetic (PK) characteristics of Motpoly XR in relation to Vimpat were not designed to establish an extensive safety profile; however, these studies did not raise any new safety concerns.

Motpoly XR provides an obvious potential benefit over an immediate release formulation of LCM due to the once daily dosing, which will likely enhance compliance and may attenuate adverse events associated with a higher C_{max} or the fluctuation of plasma concentrations throughout a 24-hour period. Although the sponsor only proposed an adult indication for Motpoly XR, the available capsule strengths also allow for dosing in pediatric patients weighing at least 50 kg, and so this pediatric indication will be included in labeling. Given the similarity in safety profile and PK findings to LCM, Motpoly XR merits approval for the indication of treatment of POS in adult and pediatric patients weighing at least 50 kg. Although Motpoly XR has the potential to attenuate some C_{max}-associated adverse events, the small safety database provided in this application do not support safety-related labeling changes, and the most serious risks identified in the "Warnings and Precautions" section of the label should remain unchanged.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Despite current approved treatments, many patients with partial-onset seizures (POS) continue to have "breakthrough" and/or refractory seizures. • Refractory seizures are seizures which persist despite adequate trials of two or more antiseizure medications (ASMs). • Breakthrough and refractory seizures increase the risk of life-threatening conditions such as status epilepticus and sudden unexplained death in epilepsy patients (SUDEP).	There is continued need for new, effective medications for patients with POS who have refractory and/or breakthrough seizures.
Current Treatment Options	• Of the many currently available drugs for the treatment of POS, only nine are available as extended-release formulations and/or are dosed once daily. • Noncompliance and fluctuation in ASM plasma levels contribute to some patients' breakthrough seizures. • Lacosamide (LCM) is approved as Vimpat immediate release tablets, as an oral solution, and as a solution for intravenous use. Vimpat in all currently available formulations is administered twice daily. • For some patients with POS, the benefit-risk profile of a particular ASM may not be favorable due to adverse effects of the drug.	There is a continued need for new extended-release formulations of effective medications for patients with POS, especially for patients who may benefit from a particular ASM but have difficulty with compliance, adverse events that are associated with peak plasma concentrations, or breakthrough seizures which are associated with fluctuations in plasma concentrations.
Benefit	• Vimpat has been found to be effective in reducing seizure frequency in adult and pediatric patients as young as one month of age with POS. • This application provides evidence from four studies of pharmacokinetic similarities, including serum concentrations and	Motpoly XR is bioequivalent to Vimpat, an approved ASM for the treatment of POS in adult and pediatric patients 1 month of age and older. Motpoly XR is expected to have similar benefit

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	cumulative AUCs at multiple time points, between Vimpat and Motpoly XR as an adequate basis for the establishment of bioequivalence. • The approved dosing regimen of Vimpat for pediatric patients weighing 50 kg or more is the same as that for adults, except for a lower initial dose of 100 mg/day for pediatrics.	on reduction of seizure frequency as its listed drug (LD), Vimpat. Motpoly XR is appropriate for the treatment of partial-onset seizures in adults and in pediatric patients weighing at least 50 kg because Motpoly XR capsules (100 mg, 150 mg and 200 mg) are effective doses for all patients weighting 50 kg or more.
Risk and Risk Management	• The safety profile of Vimpat is well-characterized in adults and pediatric patients as young as one month of age. • The most common adverse events associated with Vimpat are diplopia, headache, dizziness, nausea, and somnolence. • Warnings and precautions associated with Vimpat include suicidal behavior and ideation; dizziness and ataxia; cardiac rhythm and conduction abnormalities, particularly in patients who receive rapid infusions, who have underlying cardiac conditions, or who are on concomitant medications that affect cardiac conduction; syncope; withdrawal seizures; and drug reaction with eosinophilia and systemic symptoms. • The safety findings from the studies submitted in this application did not raise concerns of new or increased severity of adverse events with Motpoly XR as compared with the known safety profile of Vimpat.	With establishment of bioequivalence between Motpoly XR and Vimpat, the safety risks of Motpoly XR are expected to be the same as those noted for the LD, Vimpat. There were no new significant adverse events observed in the trials using Motpoly XR that are not already reported in current approved Vimpat labeling.

2. Background and Regulatory History

In this new drug application (NDA) 216185 for Motpoly XR, the Applicant (Aucta Pharmaceuticals) is seeking approval for the treatment of partial-onset seizures (POS) in patients 17 years of age and older. The Applicant filed this application under the 505(b)(2) pathway and used Vimpat (lacosamide immediate release [IR] tablet; NDA 022253) as the LD.

Vimpat was approved for the adjunctive treatment of POS in adults initially as an immediate release tablet and an intravenous formulation in 2008, then as an oral solution in 2010. Vimpat was approved as monotherapy for the treatment of POS in adults in 2014. The extension of the indication for the treatment of POS to include pediatric patients 1 month of age and above in 2021 was based on the pediatric extrapolation of efficacy from adult data.

Vimpat was also approved in 2020 for the indication of adjunctive therapy in the treatment of primary generalized tonic clonic seizures (PGTCS) in patients 4 years of age and older. However, the Applicant is not currently seeking the PGTCS indication for Motpoly XR. Given the availability of four other ASMs approved for the PGTCS indication (lamotrigine, levetiracetam, perampanel, and topiramate), the Agency found no reason to insist that the Applicant pursue the PGTCS indication at this time.

In a Type B meeting preIND WRO in October 2018, to discuss the proposed clinical development program for lacosamide extended release (ER) capsules, the Agency advised the Applicant to compare AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$ of lacosamide ER capsules to establish the bioequivalence between lacosamide ER capsules and the LD (Vimpat).

In the pre-NDA meeting WRO in August 2021, the Agency advised the Applicant to demonstrate bioequivalence for the relevant PK parameters using the standard bioequivalence criteria (i.e., 90% confidence intervals of geometric mean ratios lying within 0.80 and 1.25) between the final to-be-marketed product and the LD, Vimpat IR tablets, to support reliance on the Agency's previous findings of efficacy and safety information from the LD.

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Martha Heimann. The OPQ review lists the entire OPQ team that was involved with the review of this application. Refer to the OPQ review for details of the product quality assessment.

The OPQ team determined that the Applicant provided adequate information to ensure the identity, strength, purity, and quality of the proposed drug product. The overall manufacturing inspection recommendation was approval for all the facilities associated with this application. The proposed labeling and labels were found to include adequate information to meet the regulatory requirements.

The OPQ review notes that the Applicant originally proposed (b) (4)

The OPQ review team recommends approval of NDA 216185 for Motpoly XR capsules 100 mg, 150 mg, and 200 mg.

4. Nonclinical Pharmacology/Toxicology

No nonclinical data were submitted in this application; no nonclinical issues arose during review of this application. Therefore, a nonclinical pharmacology/toxicology review was not conducted.

5. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was conducted by Dr. Dawei Li (primary reviewer) and Dr. Gopichand Gottipati (supervisory reviewer).

The clinical pharmacology program for Motpoly XR consisted of **four Phase 1 studies** in healthy adult volunteers assessing the single dose relative bioavailability (pilot **Study 20-VIN-0088**), the steady-state relative bioavailability (pivotal **Study 20-VIN-0095**)

between Motpoly XR capsules and the reference Vimpat IR tablets, dose linearity/proportionality (**Study 22-VIN-0340**), and food effect (**Study 21-VIN-0184**).

The primary focus of the OCP review was to evaluate the adequacy of scientific bridge between Motpoly XR capsules and the reference Vimpat IR tablets.

Scientific bridge between Motpoly XR capsules and Vimpat IR tablets

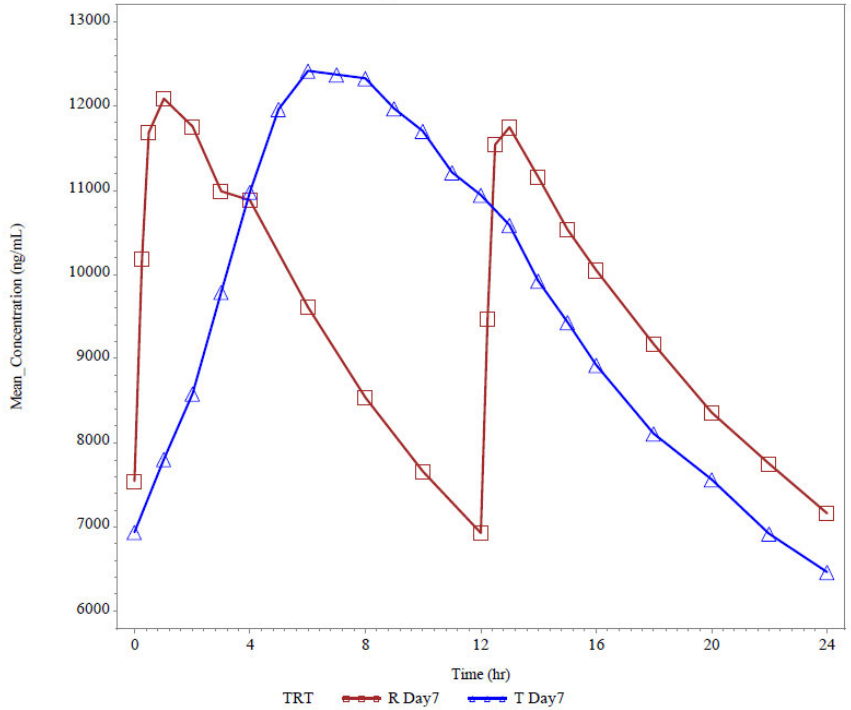
Study 20-VIN-0088 was a Phase 1 open-label, randomized, single-dose, four-treatment study to compare bioavailability of Motpoly XR capsule and Vimpat IR tablet in 24 healthy adult male subjects under **fasting** conditions. Results from **Study 20-VIN-0088**, a **pilot** comparative PK study, showed that Motpoly XR was bioequivalent to the reference Vimpat IR tablet with respect to the overall exposure ($AUC_{0\text{-}inf}$ and C_{max}).

Study 20-VIN-0095 was a Phase 1 open label, balanced, randomized, multiple-dose, two-treatment, two-sequence, two-period, oral comparative bioavailability study in healthy adult male subjects under **fasting** conditions. Thirty-five subjects were enrolled into **Study 20-VIN-0095**. The 27 subjects who completed both periods of the study were included in pharmacokinetic and statistical analysis. In this **pivotal** comparative PK study, bioequivalence was established between Motpoly XR and the LD Vimpat IR tablet at steady state with respect to $AUC_{0\text{-}24hr,ss}$; $C_{max,ss}$; and $C_{min,ss}$.

Peak concentrations occurred later for a single dose of Motpoly XR (Tmax of 7 hours) than for Vimpat IR (Tmax of 2 hours). The arithmetic mean terminal t½ value was longer for Motpoly XR (t½ of 16 hours) than Vimpat IR (t½ of 13 hours). Steady state was achieved after 4 days with Motpoly XR (compared to after 3 days of twice daily administration of Vimpat).

A plot of the steady state mean plasma levels for lacosamide for Vimpat IR (red) and Motpoly XR (blue) is presented for linear data in Figure 1. Table 1 summarizes the ratio of PK parameters and confidence intervals (C.I.).

Figure 1. Linear plot of mean plasma concentrations versus time for Vimpat IR (reference drug, R) and Motpoly XR (test drug, T) at steady state (day 7 of dosing).



Source: Clinical Study Report 20-VIN-0095, Appendix 16.2.6 Individual pharmacokinetic response data and graphs, figures on page 11 of 67.

Table 1. Ratio of the Least squares Geometric Means of PK parameters and 90% Confidence Intervals

PK Parameters (Units)	Geometric Least Squares Means and it's ratio				90% CI	Power (%)
	Test Product (T) (N=27)	Reference Product (R) (N=27)	(T/R)%	Intra-subject CV (%)		
$C_{max,ss}$ (ng/mL)	12584.623	13040.136	96.51	9.63	92.27% - 100.94%	98.49
$AUC_{0-\tau,ss}$ (hr*ng/mL)	226248.907	221131.272	102.31	3.55	100.63% - 104.03%	100.00
$C_{min,ss}$ (ng/mL)	6215.101	6660.061	93.32	6.18	90.66% - 96.05%	99.99

Source: Clinical Study Report 20-VIN-0095, Table on Page 65 of 81.

Dr. Li's independent analysis of the PK data from Study 20-VIN-0095 verified the Applicant's PK results. Dr. Li concluded that the $C_{max,ss}$, $C_{min,ss}$, and $AUC_{0-\tau,ss}$ were within the acceptable bioequivalence limits of 80.00% to 125.00%.

In response to an OCP information request, the Applicant submitted additional bioequivalence analysis results comparing the point-to-point lacosamide plasma concentrations and the partial AUC between two time-points (i.e., AUCt1-t2) to further examine the plasma profile similarity.

As shown in Table 2 below, point estimates and the 90% CIs for the ratios of steady state partial AUC (AUC0-p) between two formulations were mostly within the 80-125% bioequivalence limits, except for the initial time points before 4 hours. In addition, the 90% CI for the ratios of point-to-point lacosamide plasma concentration and partial AUC between two time points (i.e., AUCt1-t2) of the 24-hour curves for the two formulations were mostly within the 80-125% bioequivalence limits, except for the initial time points before 2 hours postdose where the 90% CIs fell slightly outside the lower bioequivalence limit and few others between 6 hours and 12 hours postdose where the 90% CIs fell outside the higher bioequivalence limit. The team concluded these are expected and acceptable differences between an immediate release formulation and an extended-release formulation.

Table 2. Partial AUC at multiple time points (Study 20-VIN-0095)

AUC, ss (hr*ng/mL)	Geometric Least Square Means and Its Ratio			Calculated 90% confidence interval	Power (%)
	Test Product (N = 27)	Reference Product (N = 27)	(T/R) %		
AUC0 – 0.5, ss (hr*ng/mL)	3467.966	4751.964	72.98	68.07-78.24	80.53
AUC0 – 1, ss (hr*ng/mL)	7164.647	10616.180	67.49	63.98-71.19	94.53
AUC0 – 1.5, ss (hr*ng/mL)	11074.197	16563.339	66.86	64.00-69.85	98.81
AUC0 – 2, ss (hr*ng/mL)	15179.879	22413.359	67.73	65.17-70.39	99.67
AUC0 – 3, ss (hr*ng/mL)	24204.453	33626.558	71.98	69.84-74.19	99.99
AUC0 – 4, ss (hr*ng/mL)	34462.151	44392.522	77.63	75.78-79.52	100.00
AUC0 – 6, ss (hr*ng/mL)	57911.476	64558.920	89.70	87.99-91.45	100.00
AUC0 – 8, ss (hr*ng/mL)	82376.651	82360.178	100.02	98.21-101.86	100.00
AUC0 – 12, ss (hr*ng/mL)	128203.815	112395.895	114.06	111.91-116.26	100.00
AUC0 – 16, ss (hr*ng/mL)	167312.544	154856.085	108.04	106.18-109.94	100.00
AUC0 – 24, ss (hr*ng/mL)	226248.907	221131.272	102.31	100.63-104.03	100.00

Source: Summary of Clinical Pharmacology, Table 7 on Page 8 of 18

Dose proportionality/linearity study 22-VIN-0340

Study 22-VIN-0340 was conducted to assess the dose proportionality of Motpoly XR capsules. This was a Phase 1, open-label, balanced, randomized, five-treatment, five-sequence, five -period cross-over, single-dose, proportionality/linearity and comparative

study of the bioavailability of Motpoly XR capsules 100 mg, 200 mg, 300 mg, 400 mg with that of Vimpat 200 mg film coated tablet in 25 healthy adult subjects under fasting conditions.

Proportionality/linearity of Cmax, AUC0-t, and AUC0-inf was assessed using a power model (Y=α*[Dose]β). A mixed effects model, allowing for random between-subject variability in the intercept and slope parameters, was used to estimate the proportionality/linearity constant, β and its 90% confidence interval. Based on calculated slope and 90 % confidence interval of slope, dose proportionality was demonstrated for both Cmax and AUC across the clinical dose range of 100 mg to 400 mg.

Food effect study 21-VIN-0184

Study 22-VIN-0340 was a Phase 1 open label, balanced, randomized, single dose, three-treatment condition, three-sequence, three-period, crossover oral bioavailability study of Motpoly XR 200 mg extended-release capsule in 18 healthy adult male subjects under fasting, fed, and fasting sprinkle condition.

High fat food and sprinkle of Motpoly XR with applesauce had no clinically meaningful impact on the PK of Motpoly XR capsules. The 90% confidence intervals of the geometric least square mean ratio (Tfast/Tfed and Tfast/TSprinkle) for Cmax, AUC0-t, and AUC0-inf were within 80-125%. The median (min - max) Tmax under fasting, fed and sprinkle conditions were 9.00 (6.00 - 12.00) hr, 10.00 (8.00 - 14.00) hr and 8.00 (7.00 - 11.00) hr, respectively.

Dr. Li concluded that this study showed that high fat food and sprinkle of the test product with applesauce had no clinically meaningful impact on the PK of Motpoly XR capsules.

Discussion of the Applicant's proposed (b) (4)

(b) (4)

(b) (4)

The Applicant concurred during labeling negotiations.

Evidence to support indication for pediatric patients weighing 50 kg or more

In its original NDA 216185 submission, the Applicant had only sought approval for the treatment of partial-onset seizures in patients 17 years of age and older because the lowest capsule strength is 100 mg and these extended-release capsules cannot be divided, crushed, or opened to accommodate the lower doses required for much of the pediatric population. However, in the labeling of the LD Vimpat, the approved dosing regimen for pediatric patients weighing 50 kg or more is the same as that for adults, except for a lower initial dose of 100 mg/day for pediatrics. Because the proposed Motpoly XR capsules (100 mg, 150 mg and 200 mg) are appropriate for the dosing regimen for pediatric patients weighting 50 kg or more, the OCP review team, after discussion with the clinical review team and consultation with the Division of Pediatric and Maternal Health, recommended expanding the patient population for the indication (treatment of partial seizures) down to pediatric patients weighting 50 kg or more. The Applicant concurred with the inclusion of this indicated population during labeling negotiations.

As discussed in Section 13 of this summary review, development of a formulation appropriate for pediatric patients weighing less than 50 kg will be a PREA postmarketing requirement.

Based on the demonstration of acceptable bioequivalence between Motpoly XR (test product) and Vimpat IR tablets (LD), the OCP review team recommends approval of this application.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

No efficacy data were submitted for review. As discussed in Section 5 of this review, the Applicant established an adequate PK bridge for Motpoly XR to the LD, Vimpat. Therefore, substantial evidence of effectiveness is provided by reference to the approved labeling and to the previously established finding of effectiveness for Vimpat .

8. Safety

Dr. Amy Kao conducted the clinical safety review of this application.

The application relies on the previous finding of an acceptable safety profile for the LD, Vimpat.

The Applicant did not conduct Phase 3 studies to support safety. Therefore, the clinical safety datasets base from the Applicant's four Phase 1 PK studies (discussed in Section 5 of this summary review) are the only sources of novel data discussed in the clinical safety review.

The Applicant performed safety analysis of the data from each of the four PK studies individually but did not provide an integrated summary of safety based on pooling of the data. Therefore, Dr. Kao combined the safety datasets to perform an independent integrated safety analysis.

Safety Population Demographics and Exposure

The Applicant defined the Safety Population as all subjects who received a dose of test (Motpoly XR) or reference (Vimpat) product.

The demographic characteristics of the population exposed to Motpoly XR (N = 96) and to the LD, Vimpat (N = 75), in these studies were homogenous; specifically, the subjects were all Asian, young adult (age range: 20 to 44 years), and male.

Dr. Kao notes that the data derived from healthy volunteers are not as informative as those derived from a study of subjects with epilepsy on concomitant antiseizure medications. However, there is a reasonable expectation that the safety for Motpoly XR will not

differ significantly from that of the LD when used in the intended population, and no obvious safety signal emerged in the population evaluated in the Phase 1 studies submitted with this NDA.

Table 3: Safety Population, Size and Denominators (all healthy adult males)*

Clinical study	Motpoly XR (N=96)	Vimpat (N=75)
Study 20-VIN-0088 (three different formulations of LCM ER)	24	24
Study 20-VIN-0095 (Motpoly XR)	29	29
Study 21-VIN-0184 (Motpoly XR fasting, fed, sprinkled)	18	0
Study 22-VIN-0340 (proportionality study)	25	22

Source: Dr. Kao's analysis of joined ADSL datasets from all studies
* A subject could have received both Motpoly XR and Vimpat within the same study. Separate exposures for a single subject are considered independent observations.

Table 4: Duration of Exposure to Motpoly XR

	Number of subjects* exposed to the study drug:	
Dosage	1 dose	7 days
Motpoly XR 100 mg	N=23	N=0
Motpoly XR 200 mg	N=40	N=0
Motpoly XR 300 mg	N=21	N=0
Motpoly XR 400 mg	N=46	N=29

Source: Dr. Kao's analysis of joined ADSL datasets from all studies
* Not all unique subjects. Separate exposures for a single subject are considered independent observations.

Deaths

No deaths occurred during these four studies.

Serious Adverse Events

There were no serious adverse events reported during these four studies.

Dropouts and/or Discontinuations Due to Adverse Effects

One subject in Study 20-VIN-0088 was withdrawn from the study by the investigator due to a facial abrasion which did not appear to be related to the administration of study drug. Two subjects in Study 22-VIN-0340 were withdrawn; one after vomiting and one after vomiting and loose bowel movement which was described as "gastroenteritis."

Treatment Emergent Adverse Events and Adverse Reactions

In the four Phase 1 studies, 12 total AEs (in 12 subjects) occurred as displayed in Table 5. Five subjects (5.2% of the 96 total subjects who received Vimpat) had an AE after most recently having received the LD, Vimpat; seven subjects (9.3% of the 75 total subjects who received Motpoly XR) had an AE after most recently having received Motpoly XR. Because there was an adequate time between exposures to make carryover effects unlikely, separate exposures for a single subject are considered independent observations. As indicated in Table 5 by italics, several of the AEs with reference to one of these two drugs are unlikely to be attributable to that drug. After subtracting these AEs, the number of patients who experienced an AE after most recently having received Vimpat or Motpoly XR is essentially the same (three subjects [3.1% of the 96 total subjects] after Vimpat and four subjects [5.3% of the 75 total subjects] after Motpoly XR).

Pruritus occurred in one subject who had most recently received Vimpat and in two subjects who had most recently received Motpoly XR.

Table 5: Adverse Events* by System Organ Class and Preferred Term, All Studies

System Organ Class	Preferred Term	Vimpat	Motpoly XR
CARDIAC DISORDERS	*BRADYCARDIA*	0	*1*
	ELECTROCARDIOGRAM QT SHORTENED	*1*	*0*
	HEART RATE INCREASED		
	fasting	1	0
	fed	*0*	*1*
GASTROINTESTINAL DISORDERS	BILIRUBIN CONJUGATED INCREASED	0	1
	GASTROENTERITIS	*1*	*0*
	VOMITING	0	1
NERVOUS SYSTEM DISORDERS	DIZZINESS	1	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	PRURITUS	1	2
	SKIN ABRASION	*0*	*1*
TOTAL		**5**	**7**

Sources: Dr. Kao's analysis of ADAE datasets from all studies
* Events which are italicized are those which, based on independent review by Dr. Kao, appear to not be an AE (electrocardiogram QT shortened) or is highly unlikely to be an adverse reaction to the treatment due to the timing of the AE in relation to dose administration (bradycardia; heart rate increased, fed; gastroenteritis; skin abrasion)

Dr. Kao notes that some of the AEs (bradycardia, increased heart rate, vomiting, and dizziness) are known potential AEs for LCM which are discussed in the currently approved Vimpat labeling. Pruritus, which occurred in three subjects, making it the most common AE in this safety population, has not been noted with Vimpat; however, rash, hypersensitivity, and urticaria are noted in the approved label for Vimpat. Dr. Kao concludes that since current approved labeling includes symptoms associated with mild hypersensitivity and would prompt prescribers to take note of a complaint of pruritus as a symptom associated with LCM exposure,

and therefore a labeling change is not needed.

Dr. Kao's clinical review discusses a healthy volunteer in this study who experienced new, asymptomatic, conjugated hyperbilirubinemia (including elevated unconjugated bilirubin) with normal transaminases at end-of-study, after having received three single doses of Motpoly XR and two doses of Vimpat IR tablets separated by 12 hours, with washout periods of 5 to 9 days between study periods/dose administration. An adverse reaction of hyperbilirubinemia in this context would be idiosyncratic, *i.e.*, not in the context of a constant, steady-state exposure. Elevated bilirubin has not been noted with Vimpat and is not included in the approved label; however, the current approved Vimpat labeling discusses abnormalities in liver function tests in the context of potential hypersensitivity and notes that patients should be instructed to report signs and symptoms of liver toxicity such as fatigue, jaundice, and dark urine, which encompasses signs and symptoms consistent with hyperbilirubinemia. Without a clear pathogenic mechanism or further information about the course of this subject, the relationship of this event to Motpoly XR is unclear, and inclusion of hyperbilirubinemia in labeling is not warranted.

TEAE Severity

Most AEs (10/12; 83%) reported in these studies were designated as "mild." The two AEs which were designated as "moderate" severity appeared unlikely to be drug-related, skin abrasion (recognized by the investigator 7 days after most recent dose administration of Vimpat) and gastroenteritis (occurring 26 hours after Vimpat).

Laboratory Findings

There were no clinically meaningful changes from baseline in hematology and serum chemistry laboratory tests.

Vital Signs

Dr. Kao notes that an analysis dataset relating to vital signs was not submitted. Therefore, Dr. Kao reviewed individual electrocardiogram and vital sign measurements as submitted in listing form, when related to reported AEs. She concludes these listing forms were adequate to generate safety conclusions, considering the reliance of this application on bioequivalence to the LD, Vimpat, and the extensive safety experience with Vimpat since its approval in 2008.

Electrocardiograms (ECGs)

There were no clinically meaningful changes from baseline in ECG results including no QT prolongation.

Conclusion from Safety Review

Dr. Kao's opinion is that it is possible that the reported AEs of bradycardia (seen in one subject but confounded by the subject's baseline low heart rate), pruritis, and vomiting were adverse reactions to Motpoly XR. These AEs are adequately addressed in the currently approved prescribing information of the LD, Vimpat. The case of hyperbilirubinemia did not appear to be clearly attributable to Motpoly XR, and labeling does not require modification to encourage more than routine pharmacovigilance.

Dr. Kao concluded that there were no new safety findings in the safety data for Motpoly XR from the four Phase I studies. These safety data support the approval of Motpoly XR for the proposed indication.

9. Advisory Committee Meeting

There was no advisory committee for this 505(b)(2) application because the efficacy and safety of Motpoly XR have been established through comparative bioequivalence to the LD (Vimpat).

10. Pediatrics

No pediatric data were provided. However, as noted in Section 5 of this Summary Review, the review team, in consultation with the Division of Pediatric and Maternal Health, concur that it is appropriate to provide pediatric labeling, and the Applicant agreed. The LD (Vimpat) is already approved for pediatric use from age 17 years down to 1 month old for the requested indication (partial onset seizures).

The Applicant has not developed a pediatric formulation for pediatric patients who weigh less than 50 kg. Section 13 of this Summary Review discusses the Pediatric Research Equity Act (PREA) postmarketing requirement to develop a formulation for these pediatric patients.

11. Other Relevant Regulatory Issues

No Good Clinical Practice (GCP) issues were identified in Dr. Kao's clinical review.

Dr. Kao concludes in her clinical review that the applicant has adequately disclosed financial interests/arrangements with clinical investigators.

The Office of Study Integrity and Surveillance (OSIS) was consulted for clinical and analytical site inspections for the pivotal relative bioavailability study (Study 20-VIN-0095). OSIS determined that inspections are not warranted because recent inspections of the clinical and analytical sites had been conducted and facilities were found to be in compliance.

A REMS is not required for the safe use of Motpoly XR for the treatment of POS in adult and pediatric patients weighing at least 50 kg. There is no REMS needed for the safe use of the LD, Vimpat. There are no new identified safety issues with Motpoly XR where a REMS would be necessary to mitigate identified risks.

12. Labeling

Please refer to the final negotiated product labeling. The labeling for Motpoly XR relies on the previous findings of efficacy and safety for the LD, Vimpat. Labeling negotiations with the Applicant have been completed, and the Applicant has accepted all recommended changes.

13. Postmarketing Requirements

The following is a postmarketing requirement under Pediatric Research Equity Act (PREA):

Development and validation by adult bioavailability/bioequivalence study(ies) of appropriate pediatric formulation(s) of Motpoly XR (lacosamide extended-release) to be used in pediatric patients weighing less than 50 kg.

Draft Protocol Submission:	*06/2024*
Final Protocol Submission:	*12/2024*
Study Completion:	*12/2025*
Final Report Submission:	*03/2026.*

14. Recommended Comments to the Applicant

See action letter.

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/

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