CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212839Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	212839
PDUFA Goal Date	November 21, 2019
OSE RCM #	2018-2560
Reviewer Name(s)	Lindsey W. Crist, PharmD, BCPS
Team Leader	Donella Fitzgerald, PharmD
Deputy Division Director	Jamie Wilkins, PharmD
Review Completion Date	November 19, 2019
Subject	Evaluation of Need for a REMS
Established Name	Cenobamate
Trade Name	Xcopri
Name of Applicant	SK Life Science, Inc
Therapeutic Class	Antiepileptic
Formulation(s)	Tablets for oral use: 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg and 200 mg
Dosing Regimen	

Initial Dosage	
Week 1 and 2	12.5 mg once daily
Titration Regimen	
Week 3 and 4	25 mg once daily
Week 5 and 6	50 mg once daily
Week 7 and 8	100 mg once daily
Week 9 and 10	150 mg once daily
Maintenance Dosage	
Week 11 and thereafter	200 mg once daily
Maximum Dosage	
If needed based on clinical response and tolerability, may increase by 50 mg once daily every two weeks	400 mg once daily

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity XCopri (cenobamate) is necessary to ensure the benefits outweigh its risks. SK Life Science, Inc. submitted a New Drug Application (NDA) 212839 for cenobamate with the proposed indication for the treatment of partial-onset seizures in adult patients. The risks associated with cenobamate include drug reaction with eosinophilia and systemic symptoms (DRESS), QT shortening, and class risks associated with antiepileptic agents including suicidal behavior and ideation, neurologic adverse reactions, and risk of increased seizures and status epilepticus with rapid withdrawal. The applicant did not submit a REMS with this application but proposed a risk management plan that includes routine pharmacovigilance and recommendations for labeling to address the risk of drug reaction with eosinophilia and systemic symptoms (DRESS).

The Division of Risk Management (DRISK) has determined that a REMS is not necessary to ensure the benefits of cenobamate outweigh its risks. Healthcare providers who treat epilepsy should be familiar with the risks of antiepileptics including the risk of DRESS. The risks associated with cenobamate can be communicated through labeling. A Medication Guide will be included for informing patients of the risk of DRESS, clinical features, and the appropriate management.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) XCopri (cenobamate) is necessary to ensure the benefits outweigh its risks. SK Life Science, Inc. submitted a New Drug Application (NDA) 212839 for cenobamate with the proposed indication for the treatment of partial-onset seizures in adult patients. This application is under review in the Division of Neurology 2 (DN2). The applicant did not submit a REMS with this application but proposed a risk management plan that includes routine pharmacovigilance and recommendations for labeling to address the risk of drug reaction with eosinophilia and systemic symptoms (DRESS).

2 Background

2.1 PRODUCT INFORMATION

XCopri (cenobamate), a new molecular entity[a], is an antiepileptic proposed for the treatment of partial-onset seizures in adult patients. The mechanism of action for cenobamate's antiepileptic effects is not fully understood. Cenobamate has been shown to reduce repetitive neuronal firing by enhancing the fast and slow inactivation of sodium channels and by inhibiting the persistent component of the sodium current. It is also a positive allosteric modulator of the γ-aminobutyric acid ($GABA_A$) ion channel.[1]

Cenobamate is proposed as immediate release oral tablets available in 12.5 mg, 25 mg, 50 mg, 150 mg, and 200 mg strengths. The Applicant's proposed dosage regimen includes a titration to the maintenance dose of (b) (4) mg daily; however, the review division determined that the labeled maintenance dose will be 200 mg (see Section 4). The proposed titration is summarized in Table 1

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

below. The proposed packaging includes titration packs and maintenance packs. Cenobamate will be administered in the outpatient and inpatient setting for chronic maintenance therapy for epilepsy.[b] Cenobamate is not currently approved in any jurisdiction.

Table 1. Cenobamate Titration Schedule[2]

Initial Dosage	
Week 1 and 2	12.5 mg once daily
Titration Regimen	
Week 3 and 4	25 mg once daily
Week 5 and 6	50 mg once daily
Week 7 and 8	100 mg once daily
Week 9 and 10	150 mg once daily
Maintenance Dosage	
Week 11 and thereafter	200 mg once daily
Maximum Dosage	
If needed based on clinical response and tolerability, may increase by 50 mg once daily every two weeks	400 mg once daily

Source: Adapted from proposed prescribing information for cenobamate, NDA 212839

2.2 Regulatory History

The following is a summary of the regulatory history for NDA 212839 relevant to this review:

- **11/21/2018:** NDA 212839 submission for the treatment of partial-onset seizures in adult patients received.
- **4/25/2019:** A mid-cycle communication meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that the significant safety issues and risk management approach for DRESS remain under review. The Agency also communicated safety concerns with the proposed packaging configurations.
- **08/21/2019:** A late cycle meeting was held between the Agency and the Applicant. No discussion on a REMS occurred at the meeting, however, the Agency noted that review of the risk of DRESS was ongoing.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Epilepsy is defined by recurrent seizures due to a chronic, underlying process. It is the fourth most common neurologic disorder with a worldwide prevalence of 65 million people.[3] Around 1.2% of the

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

U.S. population (3.4 million people) reported active epilepsy.[4,c] The overall mortality in patients with epilepsy is about 1.6 to 3 times higher compared with the general population.[3] Causes of death include sudden unexpected death in epilepsy (SUDEP), status epilepticus, accidents or injuries due to seizures (e.g. drowning, serious burns, motor vehicle accidents), or suicide. Patients with epilepsy may suffer from developmental delays, cognitive impairment, and comorbid mental health disorders (e.g. depression and anxiety). Uncontrolled epilepsy leads to high rates of unemployment and poor overall health status.[5,d]

Epilepsy is a complex spectrum of disorders with varying types of seizures, severity, and etiologies. The International League Against Epilepsy (ILAE) classifies seizures as focal onset, generalized onset, or unknown. The terms focal-onset or partial-onset are commonly used in clinical practice to refer to seizures that originate in one hemisphere of the brain.[6] Partial-onset seizures are the most common seizure type. Around 60% of patients diagnosed with epilepsy have partial-onset seizures.[7] Despite the approval of several antiepileptic medications, about one-third of patients have uncontrolled epilepsy.[3,8]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

There are over twenty FDA-approved antiepileptic drugs (AED). Selection of a specific AED is individualized based on seizure type, patient factors, and the safety profiles of the medications. Monotherapy with an antiepileptic medication is the preferred initial treatment strategy for epilepsy. See the Appendix for a table summarizing the approved antiepileptic agents for partial-onset seizures. As a class, many AEDs share several risks such as suicidal behavior and ideation, neurologic adverse events (e.g. as somnolence, fatigue, and impaired cognition), risk of serious skin reactions [e.g. Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)], drug rash with eosinophilia and systemic symptoms (DRESS), and risk of seizures if abruptly discontinued. Previously, several agents had a Medication Guide (MG) REMS for the risk of suicidal behavior and ideation. However, the REMS were released as the Agency determined that labeling, which includes the MG is adequate to convey the risk. This risk is currently conveyed in Section 5 Warnings and Precautions and with a MG.

If patients continue to have seizures despite AED monotherapy, adjunctive therapy may be considered. It is recommended to combine agents with different mechanisms while considering tolerability profiles. The chances of achieving seizure freedom decreases as more antiepileptic medications are added.[8,9] About 30% of epilepsy cases, particularly partial-onset seizures, are refractory to drug treatment.[8] Non-pharmacologic therapy options used in patients refractory to AEDs may include a ketogenic diet, surgery, or use of an implanted vagal nerve stimulator. There is an unmet need for safe and effective antiepileptic agents.

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

4 Benefit Assessment

The efficacy and safety of cenobamate for the treatment of POS was demonstrated in two pivotal studies YKP3089C013 and YKP3089C017. Both trials enrolled subjects with treatment resistant[e] partial onset seizures.

Pivotal trial YKP3089C013 (NCT02166111) was a phase 2, multicenter, randomized, double-blind, placebo-controlled trial with a 12-week (6-week titration and 6-week maintenance) treatment period. The trial evaluated cenobamate titrated[f] to the target dose of 200 mg/day compared to placebo. Pivotal trial YKP3089C017 (NCT02535091) was a phase 3, multicenter, randomized, double-blind, placebo-controlled dose-response trial with an 18-week (6-week titration and 12-week maintenance) treatment period. Subjects were randomized in a 1:1:1:1 ratio to placebo or cenobamate 100 mg, 200 mg, or 400 mg.[g] Both trials had an 8-week period to assess baseline seizure frequency. The primary endpoint for both was the percent change from baseline in seizure frequency (simple partial with motor component, complex partial, secondarily generalized tonic-clonic) per 28 days during the double-blind treatment period. Secondary endpoints included responder rates of ≥50%, ≥75%, ≥90%, and 100% reduction in seizure frequency during the double-blind treatment period and maintenance phase.

Results:

In pivotal trial YKP3089C013, a total of 222 subjects were enrolled with 113 randomized to cenobamate and 109 to placebo. The intention to treat population included 113 subjects in the cenobamate group and 108 subjects in the placebo group. Treatment with cenobamate resulted in a statistically significant difference in the primary endpoint of percent change from baseline in seizure frequency compared to placebo (see Table 2). Cenobamate resulted in a higher percent of subjects with a ≥50% reduction from baseline in seizure frequency during the double-blind treatment period than placebo [cenobamate 50.4% (57/113) vs. placebo 21.6% (22/108)].

In pivotal trial YKP3089C017, a total of 437 subjects were enrolled and randomized to one of four treatment groups: placebo (N=108), cenobamate 100 mg/day (N=108), cenobamate 200 mg/day (N=110), or cenobamate 400 mg/day (N=111). The modified intention to treat population consisted of placebo (N=106), cenobamate 100 mg/day (N=108), cenobamate 200 mg/day (N=109), and cenobamate 400 mg/day (N=111)]. There was a statistically significant difference in the primary endpoint of percent

[e] Subjects with POS were eligible if seizures were not controlled despite treatment with 1-3 concomitant AEDs.

[f] The titration regimen for this trial included 50 mg/day for 2 weeks, 100 mg/day for 2 weeks, 150 mg/day for 2 weeks, and then 200 mg/day for 6 weeks.

[g] The initial protocol consisted of an initial dose of 100 mg with weekly increases by 100 mg to the target dose. The titration regimen was modified after the first nine patients were enrolled due to higher than expected discontinuation rates and dose reductions. The modified titration consisted of an initial dose of 50 mg and a slower dose titration of increasing by 50 mg per week. The target doses depended on assigned treatment group. After reaching 200 mg, the titration could be increased to 100 mg per week for those patients assigned to the 400 mg treatment arm.

change from baseline in seizure frequency per 28 days in the treatment period compared to placebo for all cenobamate doses. The results are summarized in Table 2 below. A higher percentage of patients with ≥50% reduction from baseline in seizure frequency in the double-blind period occurred in all cenobamate dose groups compared to placebo (40.7% for 100 mg/day, 57.8% for 200 mg/day, 60.4% for 400 mg/day vs 21.7% for placebo).

Table 2. Percent Change from Baseline in Seizure Frequency per 28 Days in the Treatment Period[10]

	N	Median Percent Change from Baseline in Seizure Frequency per 28 Days (%)[t]	p-value (compared to placebo)
Study YKP3089C013			
Placebo	108	-21.5	--
200 mg/day	113	-55.6	< 0.0001*
Study YKP3089C017			
Placebo	106	-24.3	--
100 mg/day	108	-36.3	0.006*
200 mg/day	109	-55.2	< 0.001*
400 mg/day	111	-55.3	< 0.001*

* Statistically significant compared to placebo

[t] A negative percent change from baseline in seizure frequency indicates reduction in seizure frequency from baseline.

The clinical review team concluded that the pivotal trials support the efficacy for cenobamate for partial onset seizures.[10,11,h] The clinical reviewer commented that the dose response for the primary endpoint appeared flat between the 200 mg (-55.2%) and 400 mg dose (-55.3%). Based on these results, the clinical reviewer is recommending a maintenance dose of 200 mg. Dose escalation to 400 mg is acceptable based on individual clinical response and tolerability.[11]

5 Risk Assessment & Safe-Use Conditions[i]

A total of 2564 subjects have been exposed to at least one dose of cenobamate during the clinical development program (N=1945 subjects with partial onset seizures and N=619 healthy subjects).[12] The primary safety data for cenobamate in patients with partial-onset seizures is based on pooled data from the two double-blind, placebo-controlled trials, YKP3089C013 and YKP3089C017. The double-blind pool consisted of 442 cenobamate-treated subjects and 216 placebo-treated subjects. Both trials also have ongoing, long-term open-label extensions (LT OLE) for additional supportive safety data (referred to as LT OLE pool, N=504). The ongoing, Phase 3 open-label safety trial YKP3089C021 provided additional

[h] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[i] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

safety data for patients using a lower initial dose and slower titration schedule (n=1340). Additional supportive trials included 22 phase 1 studies in healthy volunteers and special populations and a phase 2a single dose, pharmacodynamic study in patients with epilepsy.

In the double-blind pool, 64.5% (285/442) of subjects receiving cenobamate experienced a treatment-related AE compared with 44% (95/216) of subjects receiving placebo. Treatment-related AEs increased with dose. Many of the adverse events reported were consistent with the class effects of antiepileptics. Cenobamate-treated subjects had higher rates of neurologic adverse events compared to placebo in the double-blind safety population. Neurologic adverse events increased in a dose-dependent manner which is consistent with other antiepileptic agents. A small number of cenobamate-treated patients experienced suicidal behavior and suicidal ideation, although the incidence was similar to other antiepileptic agents. This risk is a class effect of antiepileptic agents and will be communicated in labeling as a Warning and Precaution for cenobamate.

A higher number of cenobamate-treated subjects (13.1%) experienced an adverse event that resulted in study drug discontinuation than in the placebo treated patients (4.2%). Adverse events that resulted in discontinuation of cenobamate were ataxia (N=7), dizziness (N=7), somnolence (N=6), nystagmus (N=3), vertigo (N=3), and diplopia (N=2). The number of subjects with adverse events that led to study drug discontinuation increased with higher cenobamate doses.

5.1 SERIOUS ADVERSE EVENTS[j]

5.1.1 Deaths

There were a total of 16 deaths in the cenobamate clinical development program. One death (classified as sudden unexplained death (SUDEP) in epilepsy) occurred prior to treatment randomization and was not considered treatment-emergent. A total of 15 treatment-emergent deaths occurred during cenobamate treatment with 10 deaths during the open label extension period of the pivotal studies, 4 deaths during the open label safety study YKP3089C021, and one death in phase 1 study YKP3089C020.[12,13]

The death in the phase 1 study was a 38 year-old female who died from eosinophilic myocarditis due to DRESS. This death was determined by the clinical reviewer as caused by cenobamate and will be discussed more in Section 5.2.1.[11] The incidence of adverse events with an outcome of death in patients treated with cenobamate in the phase 2 and 3 trials was 0.8%.[12] None of the deaths occurred during the double-blind treatment period of the trials. The causes of death included SUDEP (N=3), cardiac arrest (N=1), myocardial infarction (N=1), cardiogenic shock (N=1), sepsis (N=1), pneumonia and sepsis (N=1),

[j] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

hypovolemic shock (N=1), laryngospasm (N=1), traumatic intracranial hemorrhage (N=1), completed suicide (N=2[k]), and road traffic accident (N=1). The clinical reviewer noted that the observed SUDEP rate in the development program was comparable to other refractory epilepsy populations.[11] The clinical reviewer reviewed the cases of completed suicide and determined that only one of the cases had a possible temporal relationship. However, he concluded that suicide risk is a known class effect of AEDs and that "a single case with possible temporal relationship does not define a change in this safety risk". The clinical reviewer concluded that there was an absence of a clear, causal relationship in all deaths except the subject that developed DRESS.[11]

5.1.2 Nonfatal Serious Adverse Events

There were 25 patients (5.7%) treated with cenobamate with at least 1 serious adverse event (SAE) compared to 10 patients (4.6%) treated with placebo in the double-blind pool. Across the cenobamate dose groups, SAEs occurred in 10 subjects (9.3%) in the cenobamate 100 mg group, 7 subjects (3.1%) in the cenobamate 200 mg group, and 8 subjects (7.2%) in the cenobamate 400 mg group. Table 3 summarizes the SAEs by system

Table 3. Serious Adverse Event (SAE) Reports in Primary Safety Analysis by SOCs[11]

SOC	Cenobamate (N of SAE)			Placebo (N of SAE)
	100 mg	200 mg	400 mg	
Ear and Labyrinth Disorders	--	--	1	--
Gastrointestinal Disorders	--	--	--	1
Immune System Disorders	--	1	--	--
Infections and Infestations	--	1	--	2
Injury, Poisoning and Procedural Complications	4	2	2	2
Investigations	--	--	3	1
Musculoskeletal and Connective Tissue Disorders	1	--	--	--
Nervous System Disorders	4	2	8	4
Psychiatric Disorders	3	--	--	--
Respiratory, Thoracic, and Mediastinal Disorders	1	--	--	--
Skin and Subcutaneous Tissue Disorders	--	1	--	--

Source: Adapted from Clinical Review

[k] The 120-Day Safety Update included one additional death due to suicide in the open-label phase of Study YKP3089C017.

The most common SAEs reported in the cenobamate group were in the "nervous system disorders" system order class and included seizure (N=4), ataxia (N=2), dizziness (N=2), nystagmus (N=2), hemiparesis (N=1), lethargy (N=1), somnolence (N=1), status epilepticus (N=1). SAEs in the placebo arm included seizure (N=4). Compared to placebo, non-seizure related central nervous system AEs were more common with cenobamate and increased with dose. There were 3 events in the "psychiatric disorders" category, including two events of suicidal ideation and 1 suicide attempt in the cenobamate group (100 mg) compared to none in the placebo group. There were two SAE events due to drug hypersensitivity with cenobamate treatment. One of the hypersensitivity cases was classified as DRESS in a patient on cenobamate 200 mg. The DRESS risk will be discussed more in Section 5.2.1. The clinical reviewer commented that both hypersensitivity cases are causally related to cenobamate.

In the LT OLE pool, 103 (20.4%) of patients experienced at least 1 SAE. The only SAE experienced by ≥1% of subjects was seizure (2.2%). In Study YKP3089C021, SAEs were reported by 13.3% (11/83) of subjects in the cenobamate/phenytoin group, 10.8% (4/37) in the cenobamate/phenobarbital group, and 10.7% (130/1220) in the cenobamate/other AEDs group.[12] The most common SAE reported was seizure reported by 1.2% of patients in the cenobamate/phenytoin and cenobamate/phenobarbital groups and 1.6% in the cenobamate/other AEDs group.

5.2 ADVERSE EVENTS OF SPECIAL INTEREST

5.2.1 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Three subjects treated with cenobamate developed DRESS early in the development program. The DRESS risk at the time of identification of these cases was 3/833 or 0.36%.[14] Two cases were identified in the phase 1 pool of healthy subjects (N=535). One case included a 38-year old healthy female enrolled in the QT study (Study YKP3089C020) who died from eosinophilic myocarditis caused by DRESS. The clinical reviewer determined this death was caused by cenobamate.[11] The second case involved a 50-year-old healthy male enrolled in the phase 1 multiple ascending dose study who developed DRESS but recovered after hospitalization and discontinuation of cenobamate. The last case of DRESS occurred in the Phase 2 population. A 36-year old female with complex partial seizures enrolled in one of the pivotal phase 3 studies developed DRESS and required hospitalization. The final outcome is unknown as this patient was lost to follow up. All three subjects received a higher starting dose and titration rate than what is proposed in the labeling.[13,14]

As a result of the DRESS cases, the Sponsor and Agency agreed to a study to evaluate whether a lower starting dose and slower titration regimen would reduce the risk of DRESS.[14,15] Study YKP3089C021 (NCT02535091) is an ongoing open-label safety and pharmacokinetic[l] trial in patients with poorly controlled partial onset seizures. A lower starting dose of 12.5 mg was initiated, and the titration

[l] This study evaluated the safety and pharmacokinetics of cenobamate when administered as an adjunctive therapy with phenytoin, phenobarbital, and other antiepileptics. The purpose was to identify any specific interactions with the concurrent antiepileptic agents and characterize long-term safety. Three safety populations were analyzed including a cenobamate/phenytoin, cenobamate/phenobarbital, and cenobamate/other antiepileptics.

occurred over 12-weeks with dose increases occurring at 2-week intervals. The target dose was 200 mg but could be increased to a maximum of 400 mg/day based on clinical response. After titration, subjects entered an open-label treatment phase and were reevaluated at 12 months. In addition to changing the starting dose and titration, the protocol included additional strategies to mitigate the DRESS risk including:

- Updated informed consent
- Dispensed a laminated card to subjects with explanation of DRESS and instructions for management
- Educated the study investigators on the risk of DRESS
- Increased monitoring (increased frequency of clinic visits and follow up calls, subject skin assessment diary, local medical specialist identified for each site to assist with recognition and management)

As of the data cut-off of April 23, 2018, 1339 patients received at least 1 dose of cenobamate. No additional cases of DRESS were identified, including in the 1110 subjects that have been exposed for at least 6 months. The clinical safety reviewer's analysis confirmed that there were no additional cases of DRESS. However, he commented that the data from this open-label trial does not allow for definitive conclusions about whether this revised dosing regimen is solely responsible for the observed reduction in DRESS risk. The clinical safety reviewer notes that other possible factors may include differences in patient population studied and differences in study conduct (e.g. heightened surveillance and early discontinuation). Which of these factors impacted the observed DRESS risk is not completely understood.[14] Further, no additional cases were identified based on the data in the 120-Day Safety update which included additional data through October 1, 2018 on 1340 patients enrolled in the study.

The clinical reviewers recommend communicating the risk of DRESS in Section 5, Warnings and Precautions and including a medication guide that includes information similar to what was provided to subjects enrolled in Study YKP3089C021. The safety clinical reviewer also recommends the sponsor "closely monitor for and include as 15-day reports to the Agency any spontaneous reports suggestive of DRESS with the intention of assessing real world use risk and identification of predictive factors". Postmarketing genomic studies to identify predictive factors for DRESS are recommended.

5.2.2 QT Shortening

A QT Study consult was completed for cenobamate to review the data submitted by SK Life Sciences.[16] The effects of cenobamate on QT interval was evaluated in a placebo-controlled QT study with healthy volunteers (Study YKP3089C020). Dose-dependent effects on the QT interval were observed. A higher percentage of patients who received cenobamate (200 mg: 31% and 500 mg: 66%) had a QT interval shortening of greater than 20 milliseconds (ms) compared to placebo (6-17%). No subject had a reduction of the QTc interval below 300 ms. The available nonclinical information suggests that the observed QT shortening is mediated via blockade of the cardiac sodium channel. The reviewer recommended that the risk of QT shortening be communicated in the proposed label in Section 5 Warnings and Precautions. Cenobamate will be contraindicated in patients with Familial Short QT

Syndrome. Additional post-marketing nonclinical studies are recommended to further understanding of this risk.

6 Expected Postmarket Use

Cenobamate will be prescribed and dispensed in both the outpatient and inpatient setting. The primary prescribers are likely to be neurologists and epileptologists. These prescribers are likely to be familiar with need for slow titration of antiepileptics as well as the monitoring and management of adverse events. Cenobamate may be administered in the outpatient or inpatient setting as a chronic therapy.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for cenobamate beyond routine pharmacovigilance and labeling. SK Life Science, Inc. states that "all safe use information is currently provided within the proposed product labeling, including the proposed dosing regimen to cap the rate of DRESS".[15]

8 Discussion of Need for a REMS

The clinical reviewer recommends approval of cenobamate on the basis of the efficacy and safety information currently available.[11]

Epilepsy is a common neurologic disorder that leads to significant morbidity and mortality. Partial-onset seizures are the most common type. Despite the approval of several antiepileptic medications, about one-third of patients have uncontrolled epilepsy.

The benefit of cenobamate in treatment resistant partial onset seizures was demonstrated in two pivotal clinical studies. Pivotal trial YKP3089C013 found a statistically significant difference in the primary endpoint of percent change from baseline in seizure frequency per 28 days for the cenobamate 200 mg group compared to placebo. Pivotal trial YKP3089C017 found a statistically significant difference in the primary endpoint of percent change from baseline in seizure frequency per 28 days in the treatment period compared to placebo for all cenobamate doses studied.

Three cases of DRESS, including one fatality were observed in the clinical development program for cenobamate. No additional cases were observed in an open-label study which included additional risk management measures including evaluating a lower starting dose and slower titration regimen. The proposed label for cenobamate includes DRESS in the Warnings and Precautions section. The clinical reviewer recommends the medication guide include information for DRESS to ensure patients understand the risk and monitoring. The risk of DRESS is associated with several other antiepileptic agents and is communicated via labeling, section 5 Warnings and Precautions (see Table in Appendix). The likely prescribers of cenobamate are likely familiar with this risk and the appropriate monitoring. The risk of QT shortening will be communicated in labeling as a Warning and Precaution and as a contraindication for Familial Short QT syndrome. Additionally, the risks of suicidal behavior and

ideation, neurological adverse reactions, and the potential for increased seizure frequency upon abrupt withdrawal will be included in the Warnings and Precautions as they are for other antiepileptics.

Based on the data available, the prescribing community is expected to be familiar with the risks associated with cenobamate, which do not pose unique REMS considerations compared with the risks associated with other antiepileptics. At this time, this reviewer is not recommending a REMS for the management of the risks of cenobamate therapy.

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. In general, healthcare providers who treat epilepsy are familiar with the risks of cenobamate and the importance of patient monitoring.

Should the Division of Neurology 2 have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 References

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10.2 SUMMARY OF TREATMENT OPTIONS FOR PARTIAL ONSET SEIZURES

Drug (Approval Year)	Indication[a]	Dosage form(s)	Safety and Tolerability Issues	Risk Management Approaches
Phenobarbital *no FDA approved labeling	Treatment of partial onset seizures (POS)	Oral tablet, oral elixir, oral solution, injection	Withdrawal, risk of dependence, synergistic effects with concurrent CNS depressants or alcohol, caution in patients with depression, suicidal tendencies, or drug abuse, caution in elderly or children	Labeling – Warnings and Precautions
Dilantin Phenytoin (1953)	Treatment of partial (psychomotor, temporal lobe) seizures	Oral capsules, chewable tablets, oral suspension, injection	Cardiovascular risk with rapid infusion (injection only)	Labeling – Boxed Warning
			Withdrawal seizures/status epilepticus, suicidal behavior and ideation, multiorgan hypersensitivity reactions/drug reaction with eosinophilia (DRESS), hypersensitivity, bradycardia and cardiac arrest, hepatic injury, hematologic complications, decreased bone mineral density with chronic use, monitoring required in patients with renal/hepatic impairment or hypoalbuminemia, teratogenicity, hyperglycemia, confusion (supratherapeutic levels)	Labeling – Warnings and Precautions, Medication Guide (MG)
Mysoline Primidone (1954)	Monotherapy or adjunctive therapy for POS	Oral tablets	Suicidal ideation and behavior, withdrawal, serious dermatologic reactions including Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)	Labeling – Warnings and Precautions, MG MG only REMS – *released*
Tegretol, Carbatrol, Carbamazepine (1968)	Anticonvulsant for POS with complex symptomatology	Oral tablets, oral suspension, extended release tablets	Serious dermatologic reactions including SJS and TEN (increased risk in patients with HLA-B*1502 allele), aplastic anemia and agranulocytosis	Labeling – Boxed Warning, Contraindications
			Serious dermatologic reactions, aplastic anemia and agranulocytosis, multi-organ hypersensitivity reactions/DRESS, hypersensitivity, anaphylaxis and angioedema, suicidal behavior and ideation, anticholinergic effects, confusion/agitation, withdrawal, hyponatremia, hepatotoxicity, renal toxicity, cardiovascular abnormalities, drug interactions	Labeling – Warnings and Precautions, MG MG only REMS – *released*
Depakene Valproic acid (1973) Depakote, Depakote ER	Monotherapy and adjunctive therapy of complex POS	Oral tablets, oral capsules, oral syrup, extended release (once-	Hepatotoxicity including hepatic failure, acute liver failure in patients with mitochondrial disease, fetal risk (neural tube defects, other major malformations, and decreased IQ), life-threatening pancreatitis	Labeling – Boxed Warning, Contraindications

Divalproex sodium (1983) Depakon Valproate (1996)		daily) tablets, injection	Hepatotoxicity, Fetal toxicity, pancreatitis, suicidal behavior and ideation, hyperammonemia, hyperammonemic encephalopathy/urea cycle disorders, thrombocytopenia and bleeding, hypothermia, multiorgan hypersensitivity reactions/DRESS, drug interactions, somnolence in elderly, effect on ketone and thyroid function tests	Labeling – Warnings and Precautions, MG
Felbatol Felbamate (1993)	Monotherapy or adjunctive therapy for POS with or without generalization in adults[b]	Oral tablet, oral suspension	Aplastic anemia, hepatic failure	Labeling - Boxed Warning
			Suicidal behavior and ideation, additive effects with concurrent CNS depressants or alcohol, withdrawal, hepatic failure, aplastic anemia	Labeling – Warnings and Precautions, MG
Neurontin Gabapentin (1993)	Adjunctive therapy for POS in adults and pediatric patients 3 years and older	Oral capsules, oral tablets, oral solution	Multiorgan hypersensitivity reactions/DRESS, anaphylaxis and angioedema, caution with driving or operating heavy machinery, somnolence/sedation and dizziness, withdrawal seizures, suicidal behavior and ideation, neuropsychiatric adverse reactions (patients ages 3-12 years), tumorigenic potential (animal data), sudden and unexplained death in patients with epilepsy	Labeling – Warnings and Precautions, MG MG only REMS – *released*
Lamictal, Lamictal XR Lamotrigine (1994)	Lamictal immediate release: Adjunctive therapy for POS in patients 2 years and older Monotherapy in patients 16 years and older with POS *(conversion from single AED treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate)*	Immediate release oral tablets, chewable tablets, orally disintegrating tablets	Serious skin rashes including SJS and TEN	Labeling – Boxed Warning
			Hemophagocytic lymphohistiocytosis, multiorgan hypersensitivity reactions/DRESS, blood dyscrasias, suicidal behavior and ideation, aseptic meningitis, drug interactions (e.g. oral contraceptives, valproate), withdrawal seizures, status epilepticus, sudden explained death in epilepsy, possible ophthalmologic effects with long-term use	Labeling – Warnings and Precautions, MG MG only REMS – *released*
	Lamictal XR: Adjunctive therapy for POS with or without secondary generalization in patients 13 years and older Monotherapy in patients 13 years and older with POS *(conversion from single AED treatment)*	Extended release oral tablets		

Topamax, Qudexy XR, Trokendi XR Topiramate 1996	Topamax Immediate release: Initial monotherapy in patients 2 years and older with POS Adjunctive therapy for adults and children ages 2 to 16 years for POS	Oral tablets, sprinkle capsules	Acute myopia and secondary angle closure glaucoma, visual field defects, oligohidrosis and hyperthermia, metabolic acidosis, suicidal behavior and ideation, cognitive-related dysfunction (e.g. confusion, psychomotor slowing, difficulty with concentration), psychiatric/behavioral disturbances, somnolence/fatigue, fetal toxicity, withdrawal seizures, hyperammonemia and encephalopathy (with and without concurrent valproic acid use), kidney stones, hypothermia with concomitant valproic acid use	Labeling – Warnings and Precautions, MG MG only REMS – *released*
	Extended release: Initial monotherapy for POS in patients 2 years and older (Qudexy XR) or 10 years and older (Trokendi XR) Adjunctive therapy for POS in patients 2 years and older (Qudexy XR) or 6 years and older (Trokendi XR)	Extended-release oral capsules		
Gabitril Tiagabine (1997)	Adjunctive therapy for POS in adults and children 12 years and older	Oral tablets	Seizures in patients without epilepsy, suicidal behavior and ideation, withdrawal seizures, cognitive and neuropsychiatric adverse effects (e.g. impaired concentration, speech or language problems, confusion, somnolence/fatigue), status epilepticus, sudden unexpected death in epilepsy, weakness, serious rash including SJS and TEN, ophthalmic effects, limited experience in patients not on inducing AEDs	Labeling – Warnings and Precautions, MG MG only REMS – *released*
Keppra, Keppra XR Levetiracetam (1999)	Keppra immediate release: Adjunctive therapy for POS in adults and children 1 month and older	Immediate release oral tablets, oral solution, injection	Behavioral abnormalities and psychotic symptoms, suicidal behavior and ideation, somnolence, fatigue, asthenia, anaphylaxis and angioedema, serious dermatologic reactions including SJS and TEN, coordination difficulties, withdrawal seizures, hematologic abnormalities, increased blood pressure, increased monitoring required in pregnancy and post-partum period	Labeling – Warnings and Precautions, MG MG only REMS – *released*
	Keppra XR: Adjunctive therapy for POS in patients 12 years and older	Extended release oral tablets		
Trileptal, Oxtellar XR Oxcarbazepine (2000)	Immediate release: Monotherapy or adjunctive therapy for POS in adults Monotherapy for POS in children ages 4 to 16 years and adjunctive therapy for	Immediate release oral tablet, oral suspension	Hyponatremia, anaphylaxis and angioedema, cross hypersensitivity reaction to carbamazepine, serious dermatologic reactions including SJS and TEN (increased risk in patients with HLA-B*1502 allele), suicidal behavior and ideation, withdrawal, cognitive symptoms, somnolence/fatigue, coordination	Labeling – Warnings and Precautions, MG MG only REMS – *released*

	POS in children 2 to 16 years		abnormalities, multiorgan hypersensitivity reactions/DRESS, hematologic effects, increased monitoring through pregnancy needed, risk of seizure exacerbation	
	Oxtellar XR: Adjunctive therapy for POS in adults and children 6 to 17 years old	Extended release oral tablet		
Zonegran Zonisamide (2000)	Adjunctive therapy for POS in adults	Oral capsule	Severe sulfonamide reactions, serious skin reactions including SJS and TEN, serious hematologic events (e.g. aplastic anemia, agranulocytosis), multiorgan hypersensitivity reactions/DRESS, oligohidrosis and hyperthermia in pediatric patients, suicidal behavior and ideation, metabolic acidosis, kidney stones, renal effects, withdrawal, teratogenicity, psychiatric symptoms, psychomotor slowing, difficulty concentrating, speech/language difficulties, somnolence, fatigue, status epilepticus	Labeling – Warnings and Precautions, MG MG only REMS – *released*
Lyrica Pregabalin (2004)	Adjunctive therapy for POS in patients 1 month and older	Oral tablets, oral solution	Angioedema, hypersensitivity reactions, withdrawal, suicidal behavior and ideation, peripheral edema, dizziness, somnolence, weight gain, tumorigenic potential (animal data), ophthalmological effects, creatinine kinase elevations and rhabdomyolysis, decreased platelet count, PR interval prolongation	Labeling – Warnings and Precautions, MG MG only REMS – *released*
Vimpat Lacosamide (2008)	Oral: treatment of POS in patients 4 years and older Injection: treatment of POS in adults (17 years and older)	Oral tablet, oral solution, injection	Suicidal behavior and ideation, dizziness, ataxia, cardiac rhythm and conduction abnormalities (e.g. PR interval prolongation, atrioventricular block, ventricular tachycardia, atrial fibrillation/flutter), syncope, withdrawal, multiorgan hypersensitivity reactions/DRESS, caution in patients with phenylketonuria (oral solution)	Labeling – Warnings and Precautions, MG MG only REMS – *released*
Sabril Vigabatrin (2009)	Adjunctive therapy for refractory complex POS in patients 10 years or older who have responded inadequately to several alternative treatments[b]	Oral tablets, powder for oral solution	Permanent vision loss	REMS with elements to assure safe use; Labeling – Boxed Warning
			MRI imaging abnormalities in infants, neurotoxicity (animal data), suicidal behavior and ideation, withdrawal, anemia, somnolence and fatigue,	Labeling – Warnings and Precautions, MG

			peripheral neuropathy, weight gain, edema	
Fycompa Perampanel (2012)	Treatment of POS with or without generalized seizures in patients with epilepsy 4 years or older	Oral tablets, oral suspension	Serious or life-threatening psychiatric and behavioral adverse reactions	Labeling – Boxed Warning
			Suicidal behavior and ideation, neurologic effects (dizziness, gait disturbance, somnolence, fatigue), falls, multiorgan hypersensitivity reactions/DRESS, withdrawal	Labeling – Warnings and Precautions, MG
Aptiom Eslicarbazepine (2013)	Treatment of POS in patients 4 years and older	Oral tablets	Suicidal behavior and ideation, serious dermatologic reactions including SJS and TEN, multiorgan hypersensitivity reactions/DRESS, anaphylactic reactions and angioedema, hyponatremia, dizziness, disturbance in gait and coordination, neurologic adverse reactions (e.g. somnolence, fatigue, cognitive dysfunction, visual changes, caution with activities requiring alertness), withdrawal, drug-induced liver injury, abnormal thyroid function tests, hematologic adverse reactions	Labeling – Warnings and Precautions, MG
Briviact Brivaracetam (2016)	Oral: treatment of PO in patients 4 years of age and older Injection: treatment of POS in adult patients (16 years and older)	Oral tablet, oral suspension, injection	Suicidal behavior and ideation, neurologic adverse reactions (e.g. somnolence, fatigue, dizziness, and disturbance in coordination), psychiatric adverse reactions, hypersensitivity (e.g. bronchospasm and angioedema), withdrawal	Labeling – Warnings and Precautions, MG

[a]Indication is not a comprehensive list of all approved indications [b]Not a first-line treatment option per indication labeling

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