Cenobamate for treatment-resistant focal seizures: current evidence and place in therapy

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Journal of Central Nervous System Disease
Volume 14: 1–5

DOI: 10.1177/11795735211070209
SAGE

ABSTRACT

BACKGROUND: Cenobamate is newly approved for partial-onset seizures in adults, albeit the mechanism of its action remain poorly understood.

METHODS: This article aims to review the efficacy, safety, and tolerability of cenobamate in treating partial-onset seizures.

DATA COLLECTION: The English language articles were searched in the National Institute of Health clinical trials registry, PubMed, and the Cochrane library between 2010 and June 2021 using the keywords cenobamate, YKP 3089, and seizure, and filter "trial" was applied.

RESULTS: A total of 31 articles were retrieved. Eventually, two randomized, double-blind, multicenter clinical trials involving 659 patients were analyzed. Cenobamate has shown significant reduction in seizure frequency compared to placebo. In cenobamate group, a greater number of participants showed ≥50% reduction in seizure frequency, adverse effects, and drug discontinuation compared to placebo. Multiple drug-drug interactions with other anti-seizure drugs were also observed.

CONCLUSIONS: Based on the findings of these trials, cenobamate seems to be an attractive option for treatment-resistant partial-onset seizures; however, multiple treatment-related adverse effects and drug-drug interactions are the areas of concern.

KEYWORDS: Epilepsy, Cenobamate, YKP3089, Seizure Disorders

RECEIVED: July 17, 2021. **ACCEPTED:** December 13, 2021.

TYPE: Review

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Introduction

Epilepsy is one of the most common central nervous system (CNS) diseases, and affects approximately 50 million people globally, with an annual incidence of 5 million. It is characterized by recurrent seizures[1] that result from abnormal excessive neuronal activity in the different areas of the brain, leading to various symptoms, ranging from slight loss of attention to frank convulsions.[2] Broadly, the seizures are divided into focal, generalized, and unknown onset. Focal seizures are usually restricted to the areas of the brain associated with organic aberration, whereas generalized seizures involve both cerebral hemispheres and have numerous underlying causes.[3,4] Epilepsy is defined as the occurrence of two or more unprovoked seizures 24 hours apart. Currently, numerous drugs (phenytoin, sodium valproate, carbamazepine, levetiracetam, gabapentin, and others) are available to manage seizures.[5] The diverse mechanisms underlying these drugs include modulation of γ-aminobutyric acid-ergic (-GABAergic) activity, sodium, and calcium ion channels.[5] Despite the availability of excellent drugs, about 33% of patients do not sustain seizure control.[6] Failure to achieve sustained seizure freedom with the rational use of two anti-seizure drugs administered alone or in combination defines the drug-resistant seizure, while the seizure-free interval of >1 year defines sustained seizure freedom.[7,8] The potential causes of drug-resistant epilepsy are the inability of the drug to reach the active site (probably because of drug exporters), alteration in the target structure, and no effect on the underlying causes of seizures.[9] For optimal management, confirming the diagnosis as misdiagnosis is significant (26%), imposing various restrictions on the routine activities of the patients.[10] In addition, an increased risk of trauma, early death, poor quality of life, and psychological disturbances were recorded in patients with drug-resistant epilepsy.[11] The significant prevalence of drug-resistant epilepsy and associated co-morbidities indicate a gap in the availability of drugs and their utility, that is, multiple options are available, but the efficiency is limited. The chances of being seizure-free after using different medications in drug-resistant epilepsy are only 5–10%.[12] Hence, drugs that could be beneficial in attaining sustained seizure freedom are imperative.

Cenobamate (Xcopri™), a new molecule developed by SK Life Science Inc and Arvelle Therapeutics, could treat drug-resistant seizures effectively. The drug received its first approval by United States Food and Drug Administration (USFDA) in November 2019 to manage drug-resistant focal-onset seizures and has been recently approved by European Medicine Agency.[13,14] This review aimed to discuss the pharmacology,

Table 1. Pharmacokinetic characteristics of cenobamate.[15-17]

PARAMETERS	CENOBAMATE (5–750 MG)
AUC (μg*h/mL)	2.8–1419
C_{max} (μg/mL)	0.1–17
T_{max} (h)	0.8–4.0
V_d (L)	55–42
CL (L/h)	1.3–0.4
$T_{1/2}$ (h)	30–76

AUC, area under curve; C_{max}, Maximum concentration achieved; T_{max}, Time at which maximum concentration achieved; V_d, volume of distribution; CL, Clearance; $T_{1/2}$, Half-life of drug in plasma.

efficacy, and safety of cenobamate as an adjunct in managing drug-resistant focal-onset seizures.

Data selection

A search of Cochrane, PubMed articles, and the National Institute of Health clinical trials registry (https://www.clinicaltrials.gov) from 2010 to 2021 was conducted using the following terms: cenobamate, YKP 3089, and seizure and filter "trial." Relevant articles (randomized, double-blind clinical trials) assessing the efficacy and safety of cenobamate in drug-resistant focal seizures published in English were included in this review. Initially, a total of 31 abstracts were identified, and 23 studies remained after removal of the duplicates; among these, only 2 randomized, double-blind, clinical trials were included for final analysis.

Clinical pharmacology

Significant pharmacokinetic parameters of cenobamate at different dose ranges are listed in Table 1. The data analysis revealed that area under the curve (AUC), peak serum concentration (C_{max}), time to reach maximum serum concentration (T_{max}), and half-life ($T_{1/2}$) increased in a dose-dependent manner; however, the AUC was disproportionately higher, especially at doses above 300 mg/day.[15-17] Conversely, the value of clearance and volume of distribution decreases with increasing dose.[15] The pharmacokinetic profile was consistent among individuals belonging to different age, sex, or ethnicity groups.[16] Cenobamate is metabolized by multiple enzymes, primarily by glucuronidation (UGT2B7 and UGT2B4) and oxidation (CYP2E1, CYP2A6, and CYP2B6). In addition, CYP2C19 and CYP3A4/5 play a minor role in the metabolism of cenobamate.[15] Cenobamate inhibits CYP2C19, UGT2B7, 1A1, drug transporters (OATP1B1 and OAT3) and induces CYP2B6 and 3A4 expression during in the in vitro studies; hence, numerous drug-drug interactions (DDIs) are expected.[18] Cenobamate has shown clinically significant drug interactions with other anti-seizure drugs. The concomitant administration of cenobamate with phenytoin or phenobarbital raises the C_{max} by 70% and 34%, respectively, which is attributed to CYP2C19 inhibition.[19,20] This finding was also replicated in a population study as a reduction in phenytoin/phenobarbital dose was required due to the small number of patients treated simultaneously with cenobamate.[19] The plasma level of cenobamate reduces up to 28% with simultaneous administration of phenytoin. Clobazam is converted to its active metabolite N-desmethyclobazam by CYP3A4, and this active moiety is catabolized to its inactive form by CYP2C19; administration of cenobamate increases the plasma level of the active metabolite of clobazam.[21] The pharmacokinetic studies have shown a decline in the plasma concentration of lamotrigine, levetiracetam, and carbamazepine (up to 52%, 13%, and 24%, respectively); hence, a dose increment may be required to maintain the effectiveness of the drugs.[16,19] Conclusively, the substrates of CYP2C19 and CYP3A4 should be decreased and increased, respectively. Women must use alternative methods of contraception if co-prescribed with cenobamate and combined with oral contraceptive pills as cenobamate is a CYP3A inducer.[19] Many other potential DDIs require substantiation by clinical studies. However, only a minor effect has been noted on the steady-state concentration of cenobamate. These phenomena are multifactorial as the drug is metabolized by various enzymes, potentially compensating one another in case of inhibition or induction; this drug has not yet been widely used in real-world settings. Nonetheless, post-clinical application of the drug might give rise to DDIs. Thus, cenobamate should be used cautiously in mild to moderate renal (CrCl: 30 to <90 mL/min) and hepatic impairment (Child–Pugh A or B). Cenobamate is contraindicated in severe hepatic impairment and end-stage renal disease.

The precise mechanism underlying the beneficial effects of cenobamate is not yet elucidated. However, the inhibition of persistent Na^+ currents and allosteric modulation of the $GABA_A$ channel could be speculated as potential mechanisms.[22,23] Typically, most neurons contain voltage-gated sodium channels (VGSCs) that generate action potentials via "transient" sodium current and are active above the threshold. These transient sodium currents become active and inactive swiftly. The neurons also contain active sodium channels at a subthreshold voltage and show a minimal inactivation state, termed" persistent sodium current."[24] These channels contribute to neuronal hyperexcitability by generating steady-state sodium current.[25] Cenobamate inhibits persistent sodium current and has fewer effects on the transient sodium current, making it unique. Cenobamate is more potent in inhibiting persistent sodium current than other anti-seizure drugs, such as carbamazepine. The inactivation phase and delayed recovery in persistent VGSCs facilitate the beneficial effects of cenobamate.[22] The positive modulation of $GABA_A$ subunits by cenobamate also contributes to its efficacy. GABA is the primary inhibitory neurotransmitter in CNS and leads to hyperpolarization and increase in excitation threshold. $GABA_A$ receptor stimulation leads to phasic and tonic inhibition in CNS. The phasic inhibition is short and regulates interneuron communications, while tonic inhibition is long-lasting and regulates membrane potential.[26] Cenobamate potentiates both tonic and phasic inhibition produced by the $GABA_A$ receptor by interacting with active sites different from

Table 2. Characteristics of important clinical trials of cenobamate.[28,29]

	NCT01397968		NCT01866111			
PARAMETER	CNB200	PL	CNB100	CNB200	CNB400	PL
No. of patients	113	109	108	110	111	108
No. of females	58	51	51	56	59	50
Change in seizure frequency (%)	-55.6***	-21.5	-35.5**	-55***	-55***	-24
≥50% seizure responder rate (%)	50.4***	22.2	40*	56***	64***	25
Incidence of TRAEs (%)	59.3	45.9	57	65	83	43
Incidence of SAEs (%)	1.8	3.7	9	4	7	6
Drug discontinuation rate (%)	4.4	2.8	11	15	22	5

Dosages for CNB are mg per day. Results are presented as median changes from baseline where applicable.
CNB, cenobamate; PL, placebo; TRAEs, treatment-related adverse events; SAEs, serious adverse events.
*$P \leq .03$, ** $P = .007$, *** $P \leq .0001$ vs placebo.

benzodiazepines, which is a possible explanation of its anti-epileptic activity.[27] These two potential mechanisms might also lead to other pharmacodynamic interactions with drugs, especially CNS depressants.

Clinical trials

The USFDA approved cenobamate based on the positive findings of two significant phase II randomized, double-blind clinical trials involving a total of 659 participants (Table 2).[28,29] Both trials were at low risk of selection bias, performance bias, detection bias, and attrition bias, as assessed by the risk-of-bias assessment tool.[30] In a critical phase II randomized, double-blind, placebo-controlled, multicenter trial (NCT01397968), the efficacy of cenobamate as an adjunct to anti-seizure medications was evaluated for drug-resistant focal seizures. The trial encompassed participants of either sex belonging to the age group of 18–65 years.[28] The patients had drug-resistant epilepsy and were on 1–3 anti-epileptic medications. Initially, the patients were screened initially for 8 weeks, followed by randomization and a double-blind period of 12 weeks. The double-blind period was further divided into 2 parts, that is, 6 weeks of titration and maintenance period. During the titration phase, patients were administered 50 mg/day, and the dose was titrated upward by 50 mg/day every 2 weeks until it reached 200 mg/day. According to the definition, the patients should have >3 seizures/month, and they should not have a seizure-free interval of >21 consecutive days. The efficacy endpoints were percentage and change in seizure frequency per 28 days from the baseline and percentage of patients showing ≥50% reduction in seizure frequency during the double-blind period. The safety endpoints included the incidence of treatment-related adverse effects (TRAEs), serious adverse effects (SAEs), and the number of patients who discontinued the drug. The decline in seizure frequency was 21.5% and 55.6% ($P < .0001$), while the absolute change in median seizure frequency was −.5 and −3.7 for placebo and cenobamate groups, respectively. The response rate in placebo and cenobamate groups was 22.2% and 50.4%, respectively (odds ratio [OR] = 3.94; 95% CI: 2.14-7.24; $P < .0001$). The incidence TRAEs was more for cenobamate than placebo (59.3% vs. 45.9%), while the SAEs were found to be more in the placebo group than the cenobamate group (3.7 vs. 1.8%). The SAEs in the cenobamate group were drug hypersensitivity reactions and urinary tract infections. A large number of patients discontinued cenobamate due to the adverse effects (4.4% vs. 2.8%), such as nystagmus, drug hypersensitivity, dyspnea, tachycardia, gastroesophageal reflux disease, depression, and aggression, compared to the placebo group. All the patients included in the trial presented numerous adverse effects; nonetheless, the incidence of somnolence, dizziness, balance disorder, and nystagmus were ≥5% in all the cenobamate groups compared to that in the placebo group.

Another pivotal phase II, randomized, double-blind, multicenter trial (NCT01866111), involving 437 patients and compared cenobamate as an adjunct at various doses (100 mg, 200 mg, and 400 mg) to placebo for managing drug-resistant seizures.[29] In this trial, males and females, aged 18–70 years, taking 1–3 anti-epileptic drugs, and diagnosed with drug-resistant epilepsy, were recruited. As mentioned above, patients were initially screened for 8 weeks, followed by randomization and a double-blind period of 18 weeks. The double-blind period was divided into 2 phases: titration (6 weeks) and maintenance (12 weeks). The patients were randomized into 4 groups according to the drug dose and placebo. The dose was titrated upwards of 50 mg or 100 mg, depending on the groups. The patients should have ≥8 seizures per month and not have a seizure-free interval of >25 consecutive days. The major efficacy endpoints were percentage change from baseline in median focal seizure frequency per 28 days during the double-blind period and percentage of patients achieving ≥50% decline in seizure frequency during 12 weeks. The safety endpoints included the incidence of TRAEs, SAEs, and the number of patients who discontinued the drug. The change in seizure frequency for the placebo and 100 mg, 200 mg, and 400 mg cenobamate groups

was −24%, −35.5% (P = .007), −55% (P < .0001), and −55% (P < .0001), respectively. The responder's rate during the 12 weeks of maintenance phase for placebo and 100 mg, 200 mg, and 400 mg cenobamate groups was estimated 25%, 40% (OR = 1.97; 95% CI: 1.08-3.56; P < .03), 56% (OR = 3.74; 95% CI: 2.06-6.8; P < .0001), and 64% (OR = 5.24; 95% CI: 2.84-9.67; P < .0001), respectively. The incidence of TRAEs was 43%, 57%, 65%, and 83% in the placebo and 100 mg, 200 mg, and 400 mg cenobamate groups. Similarly, 6%, 9%, 4%, and 7% of patients displayed SAEs in the placebo and 100 mg, 200 mg, and 400 mg cenobamate groups. The major SAEs noted in different cenobamate groups were ataxia, nystagmus, suicidal ideation, seizures, and dizziness. The treatment discontinuation rate was 5%, 11%, 15%, and 22% in the 4 groups, respectively. The primary reasons for treatment discontinuation were ataxia, vertigo, nystagmus, and somnolence. Somnolence, dizziness, and headache were significant adverse events as their incidence was ≥5% in all the cenobamate groups than that in the placebo group. A substantial difference in the incidence of balance disorder, nystagmus, and ataxia from placebo (≥5%) was observed in the cenobamate 400 mg group, indicating a dose-dependence as the difference was less in smaller doses. A suicide attempt and a case of drug reaction with eosinophilia and systemic symptoms were also observed in the trial in the cenobamate group.

In a recent meta-analysis comprising the clinical trials discussed above, the proportion of patients showing a decline in seizure frequency by at least 50% decreased significantly in the cenobamate group compared to the placebo group (50.1% vs. 23.5%; RR = 2.18, 95% CI: 1.67-2.85; P < .001), which corroborated with the significantly high proportion of patients that achieved seizure freedom in the cenobamate group compared to the placebo group (16.2% vs. 4.9%; RR = 3.71; 95% CI: 1.93-7.14; P < .001). A large number of patients withdrew from the cenobamate group than the placebo group (16.7% vs. 11.1%), albeit not significantly. The treatment discontinuation rate (12.2% vs. 4.1%) and the incidence of adverse events (76.9% vs. 66.8%) were significantly higher in the cenobamate group compared to the control group.[31]

Relevance to patient care

Epilepsy ranks fifth among neurological disorders and is a chronic debilitating illness that severely affects the patients' quality of life. It is also a significant cause of disability (13.5 million) and mortality (126 055 epilepsy-related deaths in 2016).[32] Globally, about 80% of epilepsy patients reside in low-middle income countries, and approximately 75% do not receive appropriate treatment.[33] The standard mortality rate in epilepsy patients in high-income countries can be 4–15 times higher than the general population, while similar data is scarce in low-income countries.[34] Due to a significant risk of premature death, disability, and other complications, adequate seizure control is essential. Although several drugs are available, only about 70% of patients become seizure-free.[32] The issue is a major concern due to the high global prevalence and chronicity of epilepsy and drug-resistant seizures. Thus, drugs that could reduce the prevalence of drug-resistant seizures are an urgent requirement.

The combination of various anti-seizure drugs and other drugs effectuate potential DDIs. Cenobamate has been shown to increase the plasma concentration of phenytoin, phenobarbital, and active metabolite of clobazam which could precipitate toxicity. The concomitant administration of cenobamate with lamotrigine, carbamazepine, and oral contraceptive pills decreases the plasma concentration of these drugs, resulting in therapeutic failure if the dose is not modified.[19-21] Cenobamate may also have a pharmacodynamic interaction with CNS depressants, leading to SAEs. Nonetheless, cenobamate offers an advantage as it is not a victim drug of various DDIs.

As mentioned above, numerous TRAEs were reported in the trials, which could determine patient acceptability. Usually, 2–3 drugs are prescribed simultaneously in resistant seizures owing to the possibility of aggravation of adverse events. The patients must be monitored for hypersensitivity, suicidal ideation, and QT shortening. Cenobamate shows non-linear pharmacokinetics in doses >300 mg/day as the recommended dose is 12.5–200 mg/day; the risk of toxicity is lesser in standard therapeutic doses. The cenobamate should be withdrawn gradually. Although the trials mentioned above were at minimal risk of different biases and provided evidence, the number of patients (659) assessed was significantly low compared to the gravity of the illness. The open-label (extension of previous trials) and phase III trials and trials for other indications are ongoing.[35] Since the approval is based on phase II trials, the results of ongoing trials would provide information on the efficacy and safety of cenobamate. However, due to the paucity of clinical trials, comparing its efficacy to that of the existing drugs is premature.

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