Cenobamate in the management of focal-onset epilepsy in adults – practical considerations for daily practice

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SUMMARY

Introduction. Cenobamate (CNB) is a newly approved antiseizure medication in Europe. It is used as an add-on treatment for focal-onset seizures in adult patients with epilepsy that is not responding to other medications.

Aim. This report discusses the practical aspects of using cenobamate to treat adult patients with epilepsy based on current experiences.

Discussion and conclusions. Studies have shown that cenobamate is effective in reducing seizure frequency in adult patients with drug-resistant focal onset epilepsy when used as add-on therapy. It also has a high seizure freedom rate, a good treatment retention rate, and a favorable safety profile. The aspects discussed include using cenobamate in special populations and potential interactions with other drugs, management strategies to mitigate the risk of adverse reactions illustrated by a specific clinical case. Further studies involving larger patient groups are necessary to assess the drug's efficacy and safety profile, particularly in special populations and patients with other types of epileptic seizures.

Key words: cenobamate • focal epilepsy • management strategies • adverse reactions

INTRODUCTION

Cenobamate (CNB) is the latest antiseizure medication (ASM) approved in Europe for the adjunctive treatment of focal-onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least two ASMs (Ontozry. Summary of product characteristics).

CNB has a dual complementary mechanism of action. On the one hand, CNB blocks voltage-gated sodium channels; conversely, it acts as a positive modulator of gamma-aminobutyric acid (GABA-A) receptors (Nakamura et al., 2019; Sharma et al., 2020; Guignet et al., 2020). While many ASMs share these mechanisms of action, CNB nevertheless exhibits certain distinct characteristics. CNB primarily exerts inhibitory effects on the persistent sodium current and has a lesser effect on the transient sodium current. Furthermore, it is more potent in inhibiting persistent sodium current than other ASMs, such as carbamazepine. CNB potentiates both tonic and phasic inhibition produced by the GABA-A receptor by interacting with active sites different from benzodiazepines (Latimer et al., 221; Cherubini, 2012; Löscher et al., 2021). It is hypothesised that this dual mechanism of action may be responsible for the drug's efficacy by potentially preventing the generation of seizures and limiting their propagation (Anderson et al., 2014; Stafstrom, 2007; Bialer et al., 2013). Nonetheless, these two potential mechanisms and the relatively complex metabolism of CNB may lead to multiple pharmacodynamic and pharmacokinetic interactions with other drugs of varying clinical relevance (Roberti et al., 2021).

The efficacy of CNB was evaluated in two randomized, placebo-controlled, short-term studies (Krauss

et al., 2020; Chung et al., 2020; Steinhoff et al., 2020), while its safety profile was assessed in open-label trials and meta-analyses (Sperling et al., 2020; Klein et al., 2022; French et al., 2021). The studies showed high treatment retention rates, high seizure-freedom rates, and good tolerability in adult patients with uncontrolled focal-onset seizures (Lattanzi et al., 2020; Zhang et al., 2021). In addition to information from registration trials, it is also important to obtain data from real-world studies that permit a more comprehensive evaluation of drug efficacy and safety, e.g. in populations that could not be studied in randomized controlled clinical trials and long-term studies.

Even though initial post-marketing studies provide evidence for the therapeutic efficacy and favorable safety profile of CNB (Villanueva et al., 2023; Elliott et al., 2022; Peña-Ceballos et al., 2023), only limited data are available on the duration of response achieved in clinical trials and ways to optimize the dose of CNB and other ASMs used in long-term therapy to fully exploit the potential of the drug in everyday practice settings.

Since March 2023, CNB has been reimbursed in Poland for the adjunctive treatment of focal-onset seizures in adult patients with epilepsy who have not been adequately controlled despite a history of at least one add-on treatment. It is thus an early stage of treatment when the drug can be used following established principles of therapeutic management.

This study explores the practical aspects of using CNB in treating adult patients with epilepsy in light of experiences gained to date. The aspects discussed include potential interactions with other drugs and management strategies mitigating the risk of adverse reactions illustrated by a specific clinical case.

DISCUSSION

Dosage regimen

Therapy starts with the Treatment Initiation Pack containing CNB at 12.5 mg (2 weeks) and 25 mg (another 2 weeks). Next, the dose is gradually titrated every 2 weeks up to the target dose of 200 mg. Titration is performed over 12 weeks. The 200 mg/day dose was selected based on the drug's efficacy and tolerability in most patients, as determined by the findings of RCTs (Krauss et al., 2020; Chung et al., 2020). At the same time, clinical data show that the most favorable outcomes, i.e. the largest proportion of patients achieving seizure freedom, are observed during treatment with the maximum dose of 400 mg. Consequently, if seizures remain uncontrolled and the drug is well tolerated, the dose may be escalated to 400 mg at increments not exceeding 50 mg every 2 weeks. It may also be necessary to adjust the dosage of other ASMs because of dose-dependent adverse effects and potential interactions.

A post hoc analysis of a randomized trial (Krauss et al., 2020) revealed a significant reduction in seizures compared to the placebo in a proportion of patients taking doses lower than the optimal dose of 200 mg. While this effect is observed in practice (Villanueva et al., 2023), especially in patients with lower drug resistance compared to the subjects of clinical trials, it is usually recommended to gradually escalate the dose up to the optimum value unless sustained freedom of seizures has been achieved (Krauss et al., 2020; Steinhoff et al., 2021). A post hoc analysis (Rosenfeld et al., 2021) showed that while a significant reduction in seizures was observed with the CNB dose of 100 or 200 mg/day, it appears that higher doses are required for achieving seizure freedom, especially in the long term.

The drug's half-life allows CNB to be used once daily (Vernillet et al., 2020), simplifying the dosage regimen. Patients, especially those with chronic conditions, are more likely to adhere to once-weekly dosing than more frequent dosing regimens, resulting in better seizure control (Kim et al., 2020; Coleman et al., 2012; O'Rourke and O'Brien, 2017).

Gradual dose titration, over a dozen weeks or so, may be problematic, especially when the objective is to achieve seizure control quickly. This is especially relevant for patients with cluster seizures or status epilepticus, where achieving the therapeutic dose rapidly is crucial. Conversely, in patients with chronic epilepsy, especially those who have experienced adverse reactions due to rapid drug switching, a gradual dose escalation schedule may prove to be beneficial.

Adverse reactions requiring special attention

Generally, the adverse reactions reported in regulatory trials were mild to moderate, mainly including dose-dependent symptoms of somnolence, diplopia, dizziness, fatigue, and non-dose-dependent headache (Krauss et al., 2020; Chung et al., 2020; Steinhoff et al., 2020; Sperling et al., 2020). Given the mechanism of action of CNB, these adverse reactions can be expected, particularly if other medications with similar mechanisms of action or at high doses are taken concomitantly. Advising patients to take the drug before bedtime or

late in the evening may be beneficial to prevent somnolence, which is the most common adverse reaction (Steinhoff et al., 2021).

Special consideration should be given to two distinct potential adverse effects.

Drug reaction with eosinophilia and systemic symptoms (DRESS)

The current dosing regimen was introduced after three cases of DRESS syndrome, including one fatality, were identified among the first 953 participants exposed to cenobamate during early clinical development. DRESS occurred in two healthy volunteers and one patient with epilepsy. DRESS cases were associated with the initiation of CNB treatment at a high starting dose (50, 100, and 200 mg, respectively) and/or dose titration every week or faster (Sperling et al., 2020). The schedule in which treatment is commenced at a low dose (12.5 mg) and increased incrementally every 2 weeks appears to have mitigated the risk of DRESS. In another study assessing the drug's safety, no other cases of this syndrome were reported (Sperling et al., 2020). As with other ASMs, the 'start-low, go slow' titration strategy reduces the risk of hypersensitivity reactions (Zaccara et al., 2007; Hirsch et al., 2006).

While the mechanism underlying DRESS syndrome remains poorly understood, its pathophysiology involves three essential factors: genetic predisposition linked to some specific Human Leukocyte Antigen (HLA) alleles; change in the metabolic pathways of drugs, mainly aromatic antiseizure medications; and reactivation of the human herpesvirus 6 (HHV-6) leading to T-cell mediated inflammatory response, causing tissue damage (Wang and Mei, 2017; Calle et al., 2023).

The response that occurred during the initial use of CNB is not unique. At least 44 drugs have been implicated in DRESS, including antiepileptics, antibiotics, antituberculosis agents, and non-steroidal anti-inflammatory drugs. This particularly applies to the ASMs that contain an aromatic ring, i.e. carbamazepine, lamotrigine, phenobarbital, phenytoin, and oxcarbazepine (Calle et al., 2023).

It needs to be highlighted that DRESS is a rare syndrome, with an incidence of 1:10,000 to 1:1,000 in patients treated with ASMs (Bocquet et al., 1996).

DRESS syndrome is characterized predominantly by the presence of fever above 38°C, maculopapular rash, enlarged lymph nodes, internal organ involvement, and peripheral blood smear changes (eosinophilia, neutrophilia, neutropenia, thrombocytopenia, hemolytic anemia) (Bocquet et al., 1996).

It is essential to explain to patients the reasons for slow CNB dose titration, pay attention to the risk of hypersensitivity-type skin reactions, and monitor patients for adverse reactions that usually occur at the beginning of treatment (between 2 weeks and 3 months).

Given the high mortality rate among patients with DRESS syndrome, which is approximately 10%, depending on the involvement of internal organs, an accurate and quick diagnosis is essential (Wolfson et al., 2019). It is crucial to recognize the early symptoms and discontinue the medication suspected of causing them as promptly as possible. The definitive confirmation of the diagnosis and the initiation of active therapeutic measures need to be made in a specialized dermatological center. However, cooperation with a neurologist or epileptologist is important to protect the patient from the risk of exacerbation of epileptic seizures or the development of status epilepticus in association with ASM discontinuation.

In a long-term study evaluating the safety of CNB (Sperling et al., 2020), aside from skin symptoms associated with DRESS, adverse reactions involving the skin and subcutaneous tissue were relatively rare. The most common were rash, pruritus, dermatitis, and alopecia.

QT-shortening

Both RCTs (Krauss et al., 2020; Chung et al., 2020) revealed a dose-dependent shortening of the QT interval on ECG. The effect was most pronounced with the 500 mg dose exceeding the recommended dose. Consequently, CNB is contraindicated in patients with familial short QT syndrome. Also, caution should be exercised when CNB is used concomitantly with other drugs known to shorten the QT interval, such as rufinamide or primidone, as there may be synergistic effects (Zaccara, Lattanzi, 2019). However, no guidelines recommend performing an ECG as a routine procedure before initiating CNB therapy.

Special populations

A limitation of registration trials is the exclusion of specific population groups, notably individuals with severe comorbidities, on specific medications, elderly patients, or women planning pregnancy. In practice, these patients are the most challenging, especially when seizure control is difficult to achieve. Data on the use of CNB in special populations are currently limited and

rely primarily on extrapolating data from clinical trials or involving small patient samples (Villanueva et al., 2023; Elliott et al., 2022; Peña-Ceballos et al., 2023; O'Dwyer et al., 2023; Connor, 2023).

Women of childbearing potential

The management of women of childbearing potential who are not planning a pregnancy and/or use effective methods of contraception is similar to that of other women. The efficacy of hormonal contraception, such as oral contraceptives, is not guaranteed. CNB acts as a CYP3A4 inducer, which means it can potentially decrease estrogen and progestin levels by over 50% (Zhang et al., 2018). CYP3A4 induction is dose-dependent and mainly occurs with higher doses of CNB (Greene et al., 2019). Therefore, women of reproductive potential are advised to use additional or alternative non-hormonal measures of birth control during CNB treatment. Data on pregnancy in women treated with CNB are very scarce (Ontozry. Summary of product characteristics). As with all new ASMs, based on the currently available evidence, pregnancy is contraindicated in women treated with CNB. Animal studies suggest a potential adverse impact of CNB on the developing fetus (Ontozry. Summary of product characteristics). However, research in humans is needed. If an unplanned pregnancy occurs, the decision to continue or modify the treatment regimen must take into account the yet undetermined risk of congenital malformations and/or developmental disorders in the child, as well as the patient's seizure control status and other medical factors. The patient and her family must receive all information relevant to them to make an informed decision.

It is unknown whether CNB is excreted in human milk. Furthermore, there is no data on the effects of CNB on breastfed infants or lactation.

Elderly

Elderly patients are at a greater risk of adverse effects, particularly those associated with the CNS when compared to younger individuals (Motika and Spencer, 2016). Data on the efficacy and safety profile of CNB remain limited. A post hoc analysis of a phase 3 open-label trial in patients aged 65–70, who comprised slightly over 3% of the study population, found good efficacy in this age group. However, these patients were more than twice as likely to discontinue treatment because of adverse effects compared to the other study subjects (O'Dwyer et al., 2023). Adverse reactions reported in ≥20% of elderly patients included dizziness, somnolence, falls, fatigue, balance disorders, and upper respiratory tract infections. In elderly patients starting treatment with CNB, reducing the doses of concomitant ASMs may be necessary, potentially to a greater extent than in younger patients.

As with other patients, treatment should be initiated at 12.5 mg and gradually titrated. The rate of titration to the target dose, as well as the target dose itself, depends on efficacy and tolerability.

Patients with comorbidities

Prescription of appropriate therapy should be based on the understanding that roughly 50% of adults with epilepsy have comorbidities (Gaitatzis et al., 2012) and typically take multiple other medications. When introducing a new ASM, it is essential to have an in-depth knowledge of its metabolism. Similarly to other special patient populations, clinical data on the use of CNB in patients with psychiatric and somatic comorbidities are very limited.

In a small cohort of 28 patients with developmental disabilities and uncontrolled epilepsy residing in a nursing home, a significant improvement was noted after 12 months of CNB treatment in the majority of subjects. In some cases, it was possible to either reduce the dose of other ASMs or discontinue them altogether (Connor, 2017).

CNB is largely metabolized in the liver via glucuronidation and oxidation and then excreted mainly via the kidneys (Ontozry. Summary of product characteristics). Since pharmacokinetic studies have found elevated plasma levels of CNB in patients with hepatic and/or renal impairment, the CNB dose should be adjusted in these patient groups (Ontozry. Summary of product characteristics). Reduction of the target dose may be considered in patients with renal impairment if their creatinine clearance (CrCl) is <90 mL/min (Ontozry. Summary of product characteristics). CNB is not recommended in patients with CrCl below 15 mL/min and in patients with end-stage renal disease undergoing dialysis treatment.

CNB should not be used in patients with severe hepatic impairment (Ontozry. Summary of product characteristics), while the maximum recommended dose in patients with mild and moderate hepatic impairment is 200 mg/day.

The most prevalent psychiatric condition among individuals with epilepsy is depression. It exhibits a close

bidirectional relationship with both biological and psychosocial factors (Mula, 2019). The presence of mood disorders is a strong predictor of suicidal behavior.

Most ASMs are labelled with an FDA-issued warning stating that ASMs as a drug class and across all indications, including but not limited to epilepsy, may be associated with an increase in suicidal ideation or behavior (Bell et al., 2009) based on a meta-analysis of RCTs conducted before 2008. Since then, all approved ASMs have carried this warning, even though they were never evaluated in similar studies. A recent 2021 meta-analysis including CNB (Klein et al., 2021) is critical of this cautionary advice. In a long-term open-label trial assessing the safety of CNB, three cases of attempted suicide and one case of severe suicidal ideation were reported (Sperling et al., 2020). While no definitive link has been established between CNB and suicide, the FDA recommends, as with other ASMs, monitoring patients for signs of suicidal ideation and behaviors. This is very important because patients with epilepsy face an almost threefold more significant risk of suicide compared to the general population (Christensen et al., 2007). Clinicians should be especially vigilant in assessing the mental well-being of patients, even in the absence of solid evidence confirming the causal role of ASMs (Mula et al., 2013; Kanner, 2022).

Overall, in a long-term open-label trial of CNB, psychiatric adverse reactions were rarely reported and included anxiety, irritability, and depression (Sperling et al., 2020).

Pharmacological interactions

CNB is metabolized in the liver by multiple enzymes, mainly through glucuronidation via uridine 5'-diphosphate-glucuronosyltransferase 2B7 (UGT2B7) and to a lesser extent by UGT2B4, and through oxidation via cytochromes P450 (CYP) 2E1, CYP2A6, CYP2B6 and to a lesser extent by CYP2C19 and CYP3A4/5 (Ontozry. Summary of product characteristics; Roberti et al., 2021).

CNB inhibits CYP2C19, UGT2B7, 1A1, and drug transporters (OATP1B1 and OAT3) and induces CYP2B6 and 3A4 expression during in vitro studies; thus, multiple drug interactions are expected (Roberti et al., 2021; Singh, 2021; Vernillet and Kamin, 2018). Since various enzyme systems metabolize CNB, each having a relative role in the drug's metabolism, inducing or inhibiting one metabolic pathway typically has a minor impact on the overall drug clearance, which may reduce the potential clinical significance of these interactions (Motika, 2016).

Because of approved drug indications, CNB must be used as add-on therapy. This suggests that pharmacokinetic and pharmacodynamic interactions are possible in many refractory patients, who are often treated with multiple ASMs (Roberti et al., 2021). Pharmacokinetic interactions tend to occur early in the titration period, at lower doses of concomitant ASMs, and the most important involves cytochrome P450 isoenzymes. The interactions with the most significant relevance involve clobazam (CLB), phenytoin (PHT) and phenobarbital (PB), as they are metabolized by the CYP2C19 isoenzyme, of which CNB is an inhibitor (Sperling et al., 2020; Vernillet and Kamin, 2018; Vossler, 2020). Thus, increased concentrations of these drugs and potential toxic effects can be expected (Ellakary et al., 2023). Conversely, when CNB is combined with carbamazepine or lamotrigine, one might anticipate a decrease in plasma levels by approximately 23% and 21–52%, respectively (Ontozry. Summary of product characteristics). However, this does not necessarily entail clinical implications and the need for dose adjustments.

Pharmacodynamic interactions typically manifest later in the titration period at higher doses of concomitant ASMs with similar mechanisms of action. Potentially clinically significant are interactions with sodium channel blockers. This appears to be particularly relevant for lacosamide (LCM) (Smith et al., 2022), mainly when it is used at high doses.

Given the complex metabolism of CNB and many ASMs, there is a potential for both pharmacokinetic and pharmacodynamic interactions in certain combinations. Examples include lamotrigine and carbamazepine, both of which may exhibit reduced levels at the onset of treatment due to a pharmacokinetic interaction. However, as the CNB dose is escalated, there is a potential for a pharmacodynamic interaction to occur because of similar mechanisms of action. The clinical effects should continuously be assessed on a case-by-case basis.

Strategy to combine CNB with other ASMs

In patients with uncontrolled seizures, polytherapy usually involves combining ASMs, preferably with different mechanisms of action, while monitoring the tolerability and efficacy of the combined drugs. In cases where adverse reactions arise after adding a new drug to the ASMs already used, particularly if the newly added

drug has only been recently approved and therapeutic experience is limited, there is a tendency to reduce the dose or discontinue the new medication and revert to the previous treatment regimen. However, given that the reason for adding a new ASM was previous unsuccessful treatment, a more rational approach involves assessing the potential pharmacokinetic and pharmacodynamic interactions between drug combinations and, if necessary, reducing the dose(s) of the drugs already used. This approach could enhance tolerability and safety, allowing for the titration of the new ASM to a potentially effective dose and achieving seizure control (St Louis, 2009).

The consensus among experts is to recommend either reactive or proactive measures based on the specific clinical scenario (Smith et al., 2022). Reactive measures involve reducing the dose of concomitant ASMs after the occurrence of adverse reactions. They are recommended for all ASMs, but mainly drugs with a similar mechanism of action, especially when used at high doses.

Proactive measures consist of a preventive reduction in the doses of concomitant ASMs, regardless of the occurrence of adverse events, after patients reach the CNB dose of 100 mg/day or even earlier. This applies primarily to PHT, PB, CLB, and LCM (Smith et al., 2022; Steinhoff et al., 2021). In Poland, apart from LCM used in the chronic treatment of adult patients, other drugs that may necessitate dose adjustment to prevent adverse reactions are prescribed relatively infrequently.

In a post hoc analysis of a phase 3 trial, in approximately 25% of patients treated with CNB who achieved a therapeutic effect, reducing the doses of other ASMs or even discontinuing them altogether was possible (Rosenfeld et al., 2021). Also, in a Spanish study conducted under an Expanded Access Program (EAP), which allowed flexibility similar to real-life practice, the doses of concomitant medications were reduced in almost 45% of cases (Villanueva et al., 2023), which is a promising finding.

It must be highlighted that clinical management should always be based on the patient's individual circumstances.

Case description

A 36-year-old patient with drug-refractory focal-onset epilepsy of inflammatory etiology, persisting since the age of 5, participated in 2014 in a randomized, double-blind, placebo-controlled trial evaluating the efficacy of cenobamate. In the course of the disease, the patient experienced frequent focal-onset cluster seizures evolving to bilateral tonic-clonic seizures. The monthly frequency of seizures was approximately 6 to 9. At baseline, the patient was treated with oxcarbazepine (OXC) at a dose of 1,500 mg/day and valproate at 1800 mg/day.

Based on the study design, the patients randomized to the study drug received a starting dose of 50 mg, escalated at weekly intervals. After 2 weeks of treatment, the drug was well-tolerated. During this period, the patient had five typical seizures. After another 2 weeks, the patient reported two episodes of diplopia, each lasting approximately half an hour. No seizures occurred during this period. A few days into week 5 of treatment, diplopia accompanied by reduced alertness and balance disorders occurred at a daily frequency, with the onset approximately one hour after taking the medicine and lasting up to three hours. An attempt to stagger the administration of the study drug and the patient's preexisting medications was unsuccessful. Because of intolerable side effects, the drug was discontinued over a few weeks, and the patient withdrew from the study. In the 3rd week of discontinuation, the patient's seizures returned.

Considering that the only seizure-free period in the course of the patient's treatment was the time when he was receiving CNB in 2022 after the drug was approved, but before it was included in the reimbursement scheme, another attempt at CNB treatment was made. In November 2022, the patient had between 3 and 6 seizures a month. During that period, he received OXC at a dose of 900 mg/day, LCM at 300 mg/day, and brivaracetam (BRV) at 100 mg/day.

Given the high number of ASMs (three) and adverse effects related to drug interactions observed during the clinical trial, a decision was made to discontinue one of the drugs. OXC, which was probably responsible for the drug interaction, was previously used at a considerably higher dose (1,800 mg vs 900 mg/day). Several prior attempts to withdraw OXC were unsuccessful and resulted in cluster seizures followed by delusional episodes. The last drug introduced was BRV, which contributed to a reduction in seizure frequency, though the effect was insufficient. On the other hand, LCM appeared not to exhibit therapeutic efficacy. Given the potential interaction, gradual complete discontinuation of LCM before introducing CNB was advised. CNB treatment was initiated according to the recommended schedule, starting at 12.5 mg/day and escalating the dose by increments every 2 weeks up to the target 200 mg/day dose.

The drug was well tolerated. The patient has now been seizure-free for 4 months.

The patient's case serves as an illustration of how therapeutic management impacts the success of treatment. Most importantly, the significance of the starting dose and titration rate is evident. Patients participating in the clinical trial were not allowed to adjust the dose of concomitant ASMs during rapid titration of cenobamate, which was likely to have caused the adverse effects (Krauss et al., 2020). Given the potential pharmacodynamic interactions resulting from combining drugs with a similar mechanism of action via sodium channels, particularly at high doses, LCM was proactively discontinued in this patient, which was additionally validated by the lack of significant benefits. The decision was also motivated by the fact that the patient took as many as three ASMs. Withdrawing ASMs that are unnecessary and potentially harmful is an important therapeutic goal. Nonetheless, in some patients, especially those with a history of seizure exacerbation during ASM withdrawal, CNB therapy may be initiated first, and after titration to higher potentially effective doses, the ASM scheduled for discontinuation can be gradually withdrawn.

In the reported patient, the further course of treatment will be determined by the duration of seizure freedom. Some drug-resistant patients experience a phenomenon referred to as the "honeymoon effect", observed for all ASMs (Peña-Ceballos et al, 2023; Löscher and Schmidt, 2006), which may suggest the evolution of drug tolerance. Therefore, it is reasonable to anticipate that with CNB, the seizure cessation effect might also be temporary in a specific population of patients. However, the retention rates in long-term studies are promising (French et al., 2021; Sander et al., 2022; Sperling et al., 2021). The reported patient's dose may be increased above 200 mg if needed. Then, the patient will require monitoring for potential dose-dependent adverse reactions associated with CNB itself, given that CNB used at doses exceeding 300 mg exhibits non-linear pharmacokinetics (Ontozry. Summary of product characteristics; Vernillet et al., 2020). In addition, the patient may require readjustment of the doses of concomitant medications, though OXC and BRV are not currently used at high doses.

CONCLUSIONS

Evidence emerging from the studies conducted to date suggests that cenobamate is effective in reducing seizure frequency in adult patients with drug-resistant focal-onset epilepsy as add-on therapy and has a high seizure freedom rate, a good treatment retention rate, and a favorable safety profile. Treatment should be initiated at a low dose (12.5 mg once daily) and titrated up to the target therapeutic dose. This approach can significantly mitigate the risk of adverse effects, especially DRESS-type hypersensitivity reactions.

Given possible interactions, the doses of concomitant ASMs may need to be adjusted to reduce the risk of treatment failure due to adverse effects.

Further studies involving larger patient groups are needed to assess the drug efficacy and safety profile of the drug, particularly in special populations, including the elderly, patients with comorbidities, children and women of childbearing potential, and patients with other types of epileptic seizures.

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