GRHTA
Glob Reg Health Technol Assess 2025; 12: 118-129
ISSN 2283-5733 | DOI: 10.33393/grhta.2025.3341
ORIGINAL RESEARCH ARTICLE

Cost-effectiveness of cenobamate as a therapeutic alternative for the treatment of focal epilepsy in adults with inadequate seizure control

Martina Paoletti[1], Angela Ragonese[1], Luca Budassi[1], Andrea Marcellusi[2]

[1]Economic Evaluation and HTA (EEHTA-CEIS), Centre for Economic and International Studies, Faculty of Economics, University of Rome "Tor Vergata," Rome - Italy
[2]Department of Pharmaceutical Sciences (DISFARM), University of Milan, Milan - Italy

ABSTRACT

Introduction: This study assesses the cost-effectiveness of cenobamate relative to brivaracetam, lacosamide, eslicarbazepine acetate, and perampanel in the management of focal onset seizures (FOS). The objective is to determine whether cenobamate offers enhanced therapeutic benefits and economic viability.

Methods: A comprehensive cost-effectiveness analysis was performed using a lifetime horizon model that encompassed drug acquisition costs, background therapy, monitoring, and seizure management expenses. The incremental cost-effectiveness ratio (ICER) was calculated to evaluate the quality-adjusted life years (QALYs) gained from cenobamate compared to its alternatives.

Results: Findings revealed that cenobamate while incurring slightly higher initial acquisition costs, leads to significant cost offsets due to reductions in overall seizure management expenses and minimized reliance on subsequent anti-seizure medications (ASMs). Additionally, cenobamate significantly enhances patient quality of life, demonstrated by superior response rates (seizure reduction >50%) and remission rates (100% seizure reduction) compared to the analyzed comparators. The cost-effectiveness analysis established that cenobamate is dominant across all evaluated treatment options, achieving greater QALYs at a lower total cost.

Conclusion: Cenobamate represents a more effective and economically advantageous treatment for patients with FOS when compared to brivaracetam, lacosamide, eslicarbazepine acetate, and perampanel. Its capacity to improve seizure control and enhance the quality of life, alongside favorable economic implications, underscores its position as the preferred therapeutic option in this patient population.

Keywords: Anti-seizure medications, Cenobamate, Cost-effectiveness analysis, Focal onset seizures

Introduction

Epilepsy is one of the most common neurological disorders, affecting approximately 50 million people worldwide (1-3). Each year, over 5 million new cases are diagnosed, and this number is expected to rise due to increasing life expectancy and the growing proportion of individuals surviving triggering events such as birth injuries, head trauma, brain infections, and strokes (1).

Incidence rates vary significantly depending on economic development: from 40 to 60 cases per 100,000 people per year in high-income countries to 80 to 100 cases in less economically developed regions (4). In Europe, it is estimated that 6 million people have epilepsy, with more than 500,000 affected in Italy (5-8). The incidence rate in Italy is estimated to be between 33 and 57 cases per 1,000 inhabitants (1,8,9).

Epilepsy is characterized by a predisposition to recurrent, unprovoked seizures, often accompanied by neurobiological and cognitive impairments that can have psychosocial consequences (1,10). These repercussions include a significant need for healthcare, reduced quality of life, and an increased mortality rate (11). Epilepsy is classified based on the onset of seizures, which may be focal, generalized, or of unknown origin (12), with focal onset epilepsy being the most diagnosed type (1,13,14).

Epilepsy treatment primarily involves the administration of anti-seizure medications (ASMs); however, seizure control is achieved with the first ASM in only 50% of cases. Moreover, 30-40% of patients, especially those with focal onset seizures (FOS), fail to achieve sufficient seizure control despite the availability of multiple ASM options (15-17).

Cenobamate is a new adjunctive ASM that has a dual mechanism of action pairing a sodium channel block with

Received: October 14, 2024
Accepted: April 1, 2025
Published online: May 9, 2025

This article includes supplementary material

Corresponding author:
Martina Paoletti
email: martina.paoletti@uniroma2.it

GABAA positive allosteric modulation. Two phase II studies have been carried out to assess the safety and efficacy of cenobamate. C017, the pivotal phase II study, showed that cenobamate achieved unprecedented levels of seizure freedom after 12 weeks of maintenance treatment [18.7% more patients on cenobamate were seizure-free than placebo patients ($p < 0.001$)] (18). The C013 study showed that 18.4% more patients were able to achieve seizure freedom than placebo patients after 6 weeks of maintenance treatment ($p = 0.0003$) (19).

Drug resistance is defined as the failure to achieve a complete clinical response despite the use of at least two well-tolerated ASMs, appropriately selected and adequately used, with the aim of sustained seizure freedom (20). Drug-resistant epilepsy (DRE) is associated with a 10- to 15-fold increased risk of secondary mortality from traumatic injuries, drowning, suicide, and sudden unexpected death in epilepsy (SUDEP) (2). It also has a significant impact on the lives of people with epilepsy and their caregivers due to increased cognitive deficits, emotional distress, stigmatization, dependence on caregivers, reduced educational and employment opportunities, and social isolation (22-24). The economic burden of epilepsy varies considerably depending on disease severity, time to diagnosis, and, most importantly, treatment response. In fact, it is estimated that costs can triple in cases of drug resistance (25,26).

In Italy, the annual healthcare expenditure for epilepsy is estimated to be €882 million, with approximately €299 million attributable to pharmacological treatments alone (27).

Given this scenario, evaluating all available treatment options in terms of cost-effectiveness becomes essential, not only for optimal patient management but also for the efficient allocation of available resources. However, in the Italian context, the economic evaluation of this therapy is still limited or absent, making it difficult to accurately compare it with available alternatives. The objective of this study is to fill this gap by conducting the first cost-effectiveness analysis in Italy for cenobamate, a new drug prescribed as an adjunctive therapy for the treatment of FOSs with or without secondary generalization in adult patients whose epilepsy remains insufficiently controlled despite treatment with at least two other ASMs.

The most recent ASMs approved for FOS over the past decade, known as “third-generation ASMs” (brivaracetam, perampanel, lacosamide, and eslicarbazepine acetate), included treatment-refractory patients in their clinical development programs and are currently some of the most widely prescribed options. This study evaluates the incremental cost-effectiveness ratio (ICER) associated with cenobamate compared to these third-generation ASMs available in Italy.

Methods

A cost-effectiveness model already published (28) was used to assess the efficacy and costs associated with cenobamate, by evaluating treatment response, seizure frequency, mortality, adverse event rates, and treatment discontinuation rates. The model estimates quality-adjusted life years (QALYs) and total costs. The analysis was conducted from the perspective of the Italian NHS and adhered to methodological guidelines published by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (29). The population considered included adults with FOS with or without secondary generalization, whose epilepsy remained uncontrolled despite prior treatment with at least two ASMs. Baseline demographic characteristics were aligned with those of the population enrolled in the C017 study (18), a multicentre, double-blind, randomized, placebo-controlled phase 2 trial, in subjects with poorly controlled partial seizures who were on a stable treatment regimen with a median of three other anti-seizure drugs at study initiation. Age at baseline was 39.8 years, and the proportion of males at baseline was 50.6%.

A lifetime horizon (60 years) was considered to capture the chronic nature of focal epilepsy, with a 28-day cycle length. Supporting the choice of a lifetime time horizon, time-to-discontinuation data from the C017 open-label extension (OLE) study (30) shows that approximately 71% of patients remained on treatment two years after entering the OLE. Furthermore, around 60% were able to continue treatment after four years. This demonstrates that the treatment benefit of cenobamate extends over many years as patients continue to respond to therapy. In addition to the literature suggesting that a longer time horizon is preferred, the decision to choose a lifetime horizon as the base case was confirmed by clinical expert opinion.

Costs and outcomes were discounted at an annual rate of 3.0%, as recommended by national guidelines (31).

Cenobamate treatment was compared to third-generation ASMs approved and available in Italy: lacosamide, perampanel, brivaracetam, and eslicarbazepine acetate.

Model Structure

The analysis was conducted using a Markov model. The model structure, depicted in Figure 1, simulates the possible transitions of patients between health states based on their clinical response to treatment. The clinical response was expressed in terms of the percentage reduction in FOS frequency over a 28-day period compared to baseline.

In the model, patients entered the “no response” health state (defined as less than a 50% reduction in seizure frequency; these patients are considered uncontrolled) upon initiation of adjunctive ASM therapy. During treatment (with cenobamate or alternative therapy), patients could respond to therapy, transitioning to health states with higher utility. Treatment response was assessed based on the relative reduction in FOS frequency from baseline, in line with the primary and secondary endpoints of the C017 study (18). The model’s health states were:

- No response (<50% reduction in seizure frequency)
- Moderate response: responder (≥50% to <75% seizure reduction)
- High response: responder (≥75% to <90% seizure reduction)
- Very high response: responder (≥90% to <100% seizure reduction)
- Complete response: seizure-free (100% reduction in seizures)

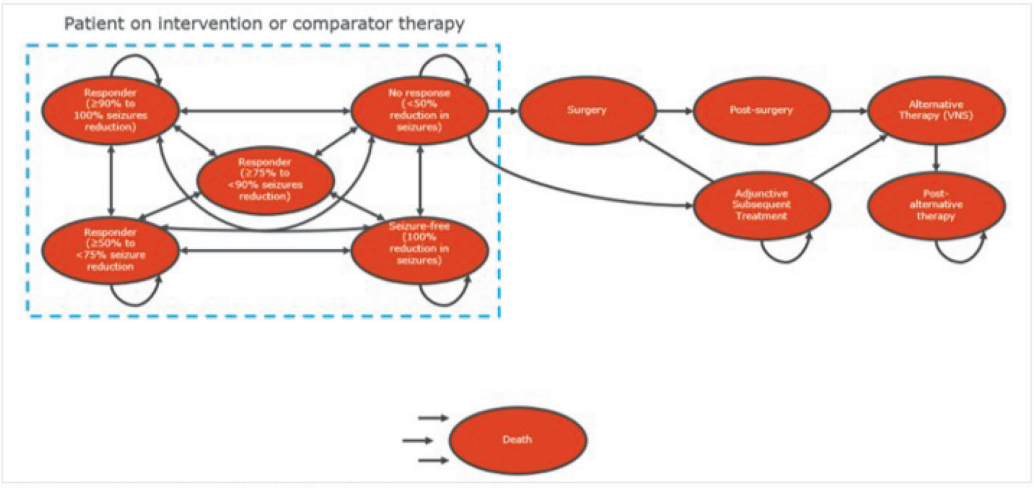

FIGURE 1 - Markov model structure.

VNS: Vagus Nerve Stimulation; ASM: anti-seizure medication

In the model, patients could either continue treatment with the drug under evaluation or discontinue it due to lack of response. If treatment with cenobamate or alternative therapies was discontinued, patients transitioned to the "adjunctive subsequent treatment" state, where they received further combinations of ASMs. If eligible for surgical procedures, patients could exit the adjunctive subsequent treatment state and move to either the surgical intervention ("surgery" health state) or "alternative therapy (VNS; vagus nerve stimulation)" health states.

Patients in the surgery state remained there for one cycle before transitioning to the "post-surgery" state, where they remained for the rest of the simulation. Patients entering the alternative therapy (VNS) state stayed for one cycle before moving to the "post-alternative therapy" state for the remainder of the simulation. Patients not eligible for surgical procedures stayed in the subsequent ASM treatment state for the entire simulation horizon. Additionally, patients could transition to the death state from any other health state in the model.

Transition probabilities between health states, represented by the arrows in Figure 1, were determined based on 28-day treatment response data.

Efficacy data

The treatment response to cenobamate was calculated based on the relative reduction in seizures compared to the baseline obtained from the C017 study (18). Specifically, the percentage of persons with epilepsy (PwE) at each response level was determined using data on seizure frequency reduction during the maintenance phase. Table 1 shows the description of each response category and the corresponding percentage of PwE treated with cenobamate over the 12-week maintenance period.

Transitions between the different rates of response were generated by observing the movement of patients between these health states at Visits 3, 5, 7, 8, and 9 of C017 (18). All patients start from the 'no response (<50% reduction)' health state at baseline. The response rate transition probabilities for cenobamate and comparator treatments from cycle 6 onwards were extrapolated using the average transition probabilities over cycles 3-5, which comprised the maintenance period.

The transition matrices applied from baseline to cycle 5 and extrapolation from cycle 6 onwards can be found in the supplementary material (Table Appendix 1).

A scenario analysis is presented in which, following the first five cycles derived from the C017 study, data from the C017 OLE is used to derive response rate transition probabilities over cycles of 84 days. Therefore, after the first five cycles, the model uses a cycle length of 84 days. There are 22 additional cycles of data from the C017 OLE, as presented in Table Appendix 2, which are then extrapolated using the average over all OLE transitions.

Due to the absence of clinical trials directly comparing cenobamate with other treatment options, a published network meta-analysis (NMA) (32) was used to determine the efficacy of the alternative ASM treatments. Efficacy outcomes were ≥50 % responder rate and seizure freedom during the maintenance period, which was modeled simultaneously using a multinomial Bayesian NMA. The analysis found that cenobamate was more effective than the other medications in reducing seizures. The NMA provided the relative risks (RR) of the comparators versus cenobamate. The RR for a ≥50% response rate was used to inform the inputs for moderate, high, and very high response health states as a conservative assumption. This assumption is cautious because by equating the high and very high response to the moderate response, we are effectively making the comparators appear more similar to cenobamate, thereby overstating their potential efficacy. This approach ensures a more cautious estimate of cenobamate's benefits relative to the comparators. For complete response, the RR for seizure freedom was applied. The RR for each alternative relative to cenobamate (Table Appendix 3) was used to adjust cenobamate's transition probabilities, generating transition matrices for the comparative treatments.

TABLE 1 - PwE distribution by response level [Source: C017 study analysis (18)]

Response Level (Health State)	Percentage of PwE (%)	Description
No response	39.85%	Uncontrolled epilepsy, less than 50% reduction in seizure rate after additional treatment.
Moderate response	21.70%	50-75% reduction in seizure rate after adjunctive treatment.
High response	15.60%	75-90% reduction in seizure rate after adjunctive treatment.
Very high response	6.70%	90-100% reduction in seizure rate after adjunctive treatment.
Complete response	16.15%	Seizure-free: 100% reduction in seizure rate.

Discontinuation Rate and Subsequent Treatment

During the simulation, PwE could discontinue treatment due to a lack of response. In the registrational study, 68.6% of PwE remained on treatment after two years; this percentage was derived from an aggregated analysis of studies C017 (18), C017 OLE (30), and C021 (33). The proportion of PwE continuing treatment beyond the registrational studies' duration was extrapolated based on Kaplan-Meier curves from the C017, C017 OLE, and C021 studies. According to the clinical opinion of experts, given the advantage that cenobamate has regarding freedom of seizure compared to other second-line ASM, the parametric distribution most suitable to reflect the duration of treatment of cenobamate in a clinical environment is expected to be flat compared to other distributions. The generalized gamma was found to be the most appropriate curve for estimating treatment interruption, taking into account the flat distribution, lower Akaike information criterion (AIC), and Bayesian information criterion (BIC) values and consistency with the duration of treatment observed in studies C017, C017 OLE, and C021 (~69% patient retention after two years). Discontinuation rates were used to estimate transition probabilities per cycle to the "Next ASM Treatment" health state. The discontinuation rates for cenobamate's alternatives were derived by generating naïve hazard ratio (HR) values based on published literature (34-38).

Additionally, PwE who did not respond to cenobamate or an alternative ASM transitioned to either the "Next ASM Treatment" health state or surgical procedures (surgery and VNS). The therapeutic effectiveness in the "Next ASM Treatment" health state and in those associated with surgical procedures was derived from literature data, expressed as the odds ratio for lack of response compared to the previous treatment line. Specifically, for the next ASM treatment's effectiveness, data were extrapolated from the Chen study (2018) (15), which reported an OR [95% CI] of 1.73 [1.56; 1.91] for the likelihood of non-response after uncontrolled epilepsy with the previous ASM.

Regarding surgical procedures, based on clinical expert evaluations, it was estimated that, annually, 2.0% and 2.7% of PwE in the "Next ASM Treatment" health state annually transitioned to the "Surgery" and "VNS" health states, respectively. The percentages of PwE experiencing a 50-100% seizure reduction or complete seizure freedom (100% reduction) after surgical procedures were derived from the following studies:

- After surgery, from the Picot et al. (2016) study (39), the rates were 5.2% and 69.0%, respectively.
- After VNS, from the Hamilton et al. (2018) study (40), the rates were 59.0% and 6.0%, respectively.

The mortality probabilities following surgical intervention (0.86% per cycle) or VNS (0.97% per cycle) were sourced from Sperling et al. (2016) (41) and Granbichler et al. (2015) (42).

Mortality

General mortality rates were derived from the 2022 Italian population data, stratified by age and gender (43). Additionally, the model accounted for the increased mortality risk associated with seizures, measured through HR from the Trinka et al. (2013) study (44), which differentiated between seizure-free PwE (HR = 1.6) and those not free from seizures (HR = 2.4).

Cost parameters

In line with the adopted analytical perspective, several cost components were identified and quantified: drug acquisition costs, background therapy, administration costs, monitoring costs, subsequent ASM treatments, seizure management, and adverse event management costs.

The drug acquisition costs were calculated considering different dosages during the titration and maintenance phases. For cenobamate, the total titration phase cost of €444.50 was based on ex-factory prices (45) after statutory reductions, with dosages obtained by SmPC (summary of product characteristics) [46]. PwE were assumed to initiate treatment with cenobamate at a dose of 12.5 mg per day, escalating every two weeks to a target dose of 200 mg per day. The average daily cost during the maintenance phase for cenobamate was calculated using the defined daily dose of 200 mg per day (47) for each 28-day cycle. The titration and maintenance schedules for alternative treatments were obtained by SmPC (48-51), and ex-factory prices after reductions were used for all treatments (45). Brivaracetam did not require a titration phase. Table 2 summarizes acquisition costs for titration and maintenance cycles across the treatments included in the analysis.

Drug consumption was adjusted based on the 96.6% compliance rate observed in the C017 study [18], which was applied to all comparators during both titration and maintenance phases.

For background therapy, it was assumed that all PwE entering the model received it. The usage frequency of each treatment in the background therapy was based on market analysis assumptions. The total cost for a 28-day cycle of background therapy was estimated using ex-factory prices (45) and dosage compositions (47). This resulted in an estimated background therapy cost of €22.99 per cycle (detailed calculations can be found in Table Appendix 4).

Administration costs were excluded since all treatment options were orally administered, and thus, administration costs were assumed to be €0.

Monitoring costs were included, differentiated between drug-related monitoring and disease follow-up. For drug monitoring, a distinction was made between the titration and maintenance phases. It was assumed that prescriptions were made during outpatient epilepsy visits, set at 3 for cenobamate and for perampanel and 2 for lacosamide and eslicarbazepine acetate. Additionally, during titration, an electrocardiogram (ECG) was assumed for lacosamide, in line with its SPC (49). During the maintenance phase, PwE were assumed to visit their general practitioner (GP) four times per year. The cost of epilepsy outpatient visits (€16.20 - Code 89.01.C) and ECG monitoring (€11.60 – Code 89.52) were sourced from the June 23, 2023, tariff decree (52). The cost of a GP visit of €76 was evaluated considering the estimated average hourly cost through the 2021 annual state account (53) and assuming the duration of the visit of one hour. Table 2 presents drug-related monitoring costs for each therapy.

Disease follow-up costs were assumed to correlate with the seizure frequency reduction achieved through treatment. Based on expert opinion, the number of neurology visits over four weeks was identified for each response category. The cost of a neurology visit was derived from the June 23, 2023, tariff decree (52). Table 2 summarizes total follow-up costs for a 4-week cycle, broken down by response category.

PwE in the "Next ASM Treatment" health state were assumed to receive one of the alternative treatments. The total cost per cycle for the subsequent ASM treatment was expressed as a weighted average of the treatment costs based on the market share distribution expected with cenobamate's introduction, as shown in Table 2. The total acquisition cost of subsequent ASM therapy was added to the background therapy cost, resulting in an overall estimate of €91.79 per cycle for subsequent treatments.

Regarding surgical procedures, the unit costs for surgery and VNS were obtained from the national tariff schedule for hospital services (54) weighted by the number of hospital discharges (55) and were €12,556 (average tariff for DRG 001 and DRG 002) and €3,531 (average tariff for DRG 007 and 008), respectively.

In addition, the model considered seizure management costs, categorized by seizure type and estimated by considering healthcare resources used. Resource consumption was divided based on seizure type (focal onset aware seizures, focal onset impaired awareness seizures, and focal to bilateral tonic-clonic seizures). Through expert consultation, the proportion of seizures requiring medical assistance was identified. Additionally, the percentage of patients experiencing seizures who utilized healthcare resources was determined, distinguishing between those who accessed healthcare services and those who required further care, as well as the percentage of patients experiencing seizures that resulted in hospitalization (Table Appendix 5). The total costs were €12.04 for focal onset aware seizures, €40.12 for focal onset impaired awareness seizures, and €202.60 for focal to bilateral tonic-clonic seizures.

Finally, the analysis included adverse event management costs. For individuals treated with cenobamate, study C021 (33) was used to determine the frequency of adverse events during the titration phase, while data from study C017 (18) were used for the maintenance phase. The adverse event

TABLE 2 - Estimated costs used in the economic model

Treatment Acquisition Cost	**Cenobamate**	**Lacosamide**	**Perampanel**	**Brivaracetam**	**Eslicarbazepine acetate**
Titration Duration (days)	84	21	56	-	21
Cost for Titration Duration (€)	€ 444.50	€ 24.58	€ 216.07	-	€ 69.18
Cost per maintenance cycle (28 days)	€ 148.18	€ 49.19	€ 108.03	€ 108.16	€ 92.24
Monitoring costs related to drug administration	**Cenobamate**	**Lacosamide**	**Perampanel**	**Brivaracetam**	**Eslicarbazepine acetate**
Total per cycle - titration phase (€)	€ 16.20	€ 44.00	€ 24.30	-	€ 32.40
Total per cycle - maintenance phase (€)	€ 23.30	€ 23.30	€ 23.30	€ 23.30	€ 23.30
Cost of disease follow-up	**No Response**	**Moderate Response**	**High Response**	**Very high Response**	**Complete Response**
Total per cycle (€)	€ 13.93	€ 8.10	€ 1.13	€ 1.13	€ 1.13
Subsequent treatments	**Cenobamate**	**Lacosamide**	**Perampanel**	**Brivacetam**	**Eslicarbazepine acetate**
Distribution of subsequent treatments (%)	5.57%	69.58%	8.04%	13.15%	3.67%

frequencies obtained from the studies were then adjusted to reflect the model's cycle length (56). The adverse event frequencies for cenobamate's comparators were calculated by applying the relative odds ratios for each treatment derived from an NMA (32). Additionally, the analysis considered adverse events associated with subsequent ASM treatments or surgery. For subsequent ASM treatments, treatment-emergent adverse event (TEAE) rates were assumed to be the same as those for cenobamate during the titration period, while adverse events for PwE undergoing surgery or VNS were sourced from the studies by Hader et al. (2013) (57) and Panebianco et al. (2015) (58) respectively. The probability of experiencing adverse events is summarized in Table Appendix 6.

Unit costs for adverse event management were derived from the June 23, 2023, tariff decree (52). Since the severity of the adverse events was unknown, the unit cost of each adverse event was assumed to be the cost of a specialist visit.

Utility values

In the model, utility values depended on the patient's health state. The utility values were derived through a mapping study based on the Short-Form Six-Dimension (SF-6D) measure (59). Within the mapping study, three key variables were included: seizure frequency in the past 28 days, seizure freedom in the past 28 days, and experience of a focal to bilateral tonic-clonic in the past 8 weeks (seizure severity). Four mapping models were explored, but the ordinary least squares (OLS) model was the best-performing regression model with the lower-scoring AIC and BIC values. All participants in the various treatment protocols in the C017 study (18) were included in the mapping analysis and categorized according to their health state in relation to treatment response. Averages of the SF-6D utility values were generated from the outputs of the mapping study.

Utility values for subsequent ASM treatments, surgery, and VNS were calculated as a weighted average of utility values related to response rates, considering the distribution of individuals across different treatment response levels.

Disutility values associated with adverse events during the titration and maintenance phases, as well as with subsequent ASM treatments, were obtained from a multivariate analysis conducted in the study by Kinderen (2016) (60). The durations of disutility were assumed based on the transitory nature of treatment-related adverse events. The utility values, disutilities, and their respective durations included in the model are summarized in Table 3.

Uncertainty

Deterministic and probabilistic sensitivity analyses were performed to explore the level of uncertainty in the model results.

The one-way sensitivity analysis (OWSA) varied each parameter individually between the upper and lower bounds of confidence intervals within pre-specified probabilistic distributions assigned to each parameter. Where the standard error was unavailable to calculate upper and lower confidence intervals, this was assumed to be ±20% of the mean value. A tornado diagram was developed to illustrate the level of uncertainty considering the incremental net monetary benefit (NMB) based on the upper and lower bounds.

Probabilistic sensitivity analysis (PSA) assigned distributions to the model parameters and ran 1,000 simulations to further explore parameter uncertainty.

The following distributions were used for the relevant parameters:

- Beta distributions were used for the clinical probabilities, resource use, and health state utilities.
- Gamma distributions were used for costs and seizure frequency.

Mean incremental results are recorded and illustrated through an incremental cost-effectiveness plane (ICEP). A cost-effectiveness acceptability curve (CEAC) was also plotted.

Results

Based on the total costs and outcome values (QALYs) generated by the model over the lifetime horizon, the incremental values of cenobamate compared to the evaluated comparators were estimated, and the ICER was calculated.

The results are presented in Table 4. Over a lifetime horizon (60 years), treatment with cenobamate yielded a QALY value of 7.54 and total costs of €151,794.72 per patient. Compared to the evaluated comparators, cenobamate resulted in lower overall costs and higher QALYs, thus demonstrating dominance over all the analyzed ASM treatments.

Table 5 shows the details of the estimate of the costs considered in the model for each treatment considered in the analysis. Despite a higher cost of acquisition and administration of the treatment, cenobamate is associated with lower total costs than comparators, thanks to the reduction in costs related to the subsequent treatments used and, above all, to crisis management.

The results obtained by including in the analysis the data of the OLE of the trial are shown in table Appendices 7 and 8.

Sensitivity analysis

The OWSA results are shown in the tornado diagram (Fig. 2). Compared to each of the third-generation ASMs included in the analysis, the utility value for non-responders was found to have the most significant impact on the cost-effectiveness results.

The results of the PSA are presented in Figure 3, which shows the cost-effectiveness plane and CEAC for each comparator. The majority of iterations shown in the cost-effectiveness plane lie in the southeast quadrant, demonstrating the cost-effectiveness of cenobamate. Also, the CEAC illustrates the probability of cenobamate being cost-effective at various willingness-to-pay thresholds.

Discussion

The increasing availability of treatment options for patients with DRE and the rising costs associated with these treatments highlight the importance of conducting detailed economic evaluations in this field (61). These evaluations are

TABLE 3 - Utility and disutility values

Health state	Value (N)	Duration (days)	Utility Value Source
Utility			
No response	0.50	28.00	[60]
Moderate response	0.57	28.00	
High response	0.61	28.00	
Very high response	0.61	28.00	
Complete response	0.65	28.00	
VNS	0.50	28.00	Assumed equals no response
Post-VNS	0.56	28.00	Calculated
Surgery	0.50	28.00	Assumed equals no response
Post- Surgery	0.61	28.00	Calculated
Subsequent ASM treatment	0.55	28.00	Calculated
Disutility			
Related to adverse events, for the titration and maintenance phase	–0.06	28.00	[61]
Related to adverse events, for subsequent ASM treatment	–0.06	28.00	
Related to voice alteration	–0.16	182.63	[72], [73]
Related to cough, dyspnea	–0.16	365.25	
Related to pain	–0.05	365.25	
Related to paresthesia	–0.01	273.94	
Related to infection	–0.11	182.63	
Related to neurological complications	–0.20	182.63	[74], [75], [76], [77]
Related to infection	–0.11	91.31	
Related to aseptic meningitis	–0.20	91.31	
Related to deep vein thrombosis/pulmonary embolus	–0.22	91.31	
Related to intracranial hematoma	–0.25	91.31	
Related to pneumonia	–0.64	91.31	
Related to CSF leakage	–0.28	91.31	
Related to hydrocephalus	–0.28	91.31	

TABLE 4 - Cost-effectiveness analysis results

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Cenobamate	151,794.72 €	7.54			
Lacosamide	167,751.43 €	6.91	–15,956.71 €	0.63	Dominant
Perampanel	174,221.54 €	6.85	–22,426.82 €	0.68	Dominant
Brivaracetam	177,385.43 €	6.82	–25,590.71 €	0.71	Dominant
Eslicarbazepine acetate	184,492.60 €	6.58	–32,697.88 €	0.95	Dominant

TABLE 5 - Results by cost category

Cost item	Cenobamate	Brivaracetam	Lacosamide	Eslicarbazepine acetate	Perampanel
Treatment cost	23,755.22 €	13,136.54 €	6,556.97 €	14,932.63 €	11,336.97 €
Cost of subsequent ASM treatments	9,160.18 €	11,539.44 €	12,152.05 €	9,668.11 €	12,413.58 €
Monitoring costs associated with administration	5,102.53 €	4,656.00 €	4,563.42 €	5,002.47 €	4,497.12 €
Follow-up cost	2,091.83 €	2,637.26 €	2,581.69 €	2,739.44 €	2,601.92 €
Seizure management cost	110,600.42 €	144,736.70 €	141,251.65 €	151,045.08 €	142,588.62 €
Adverse event management costs	1,084.54 €	679.49 €	645.65 €	1,104.86 €	783.34 €
Total	151,794.72 €	177,385.43 €	167,751.43 €	184,492.60 €	174,221.54 €

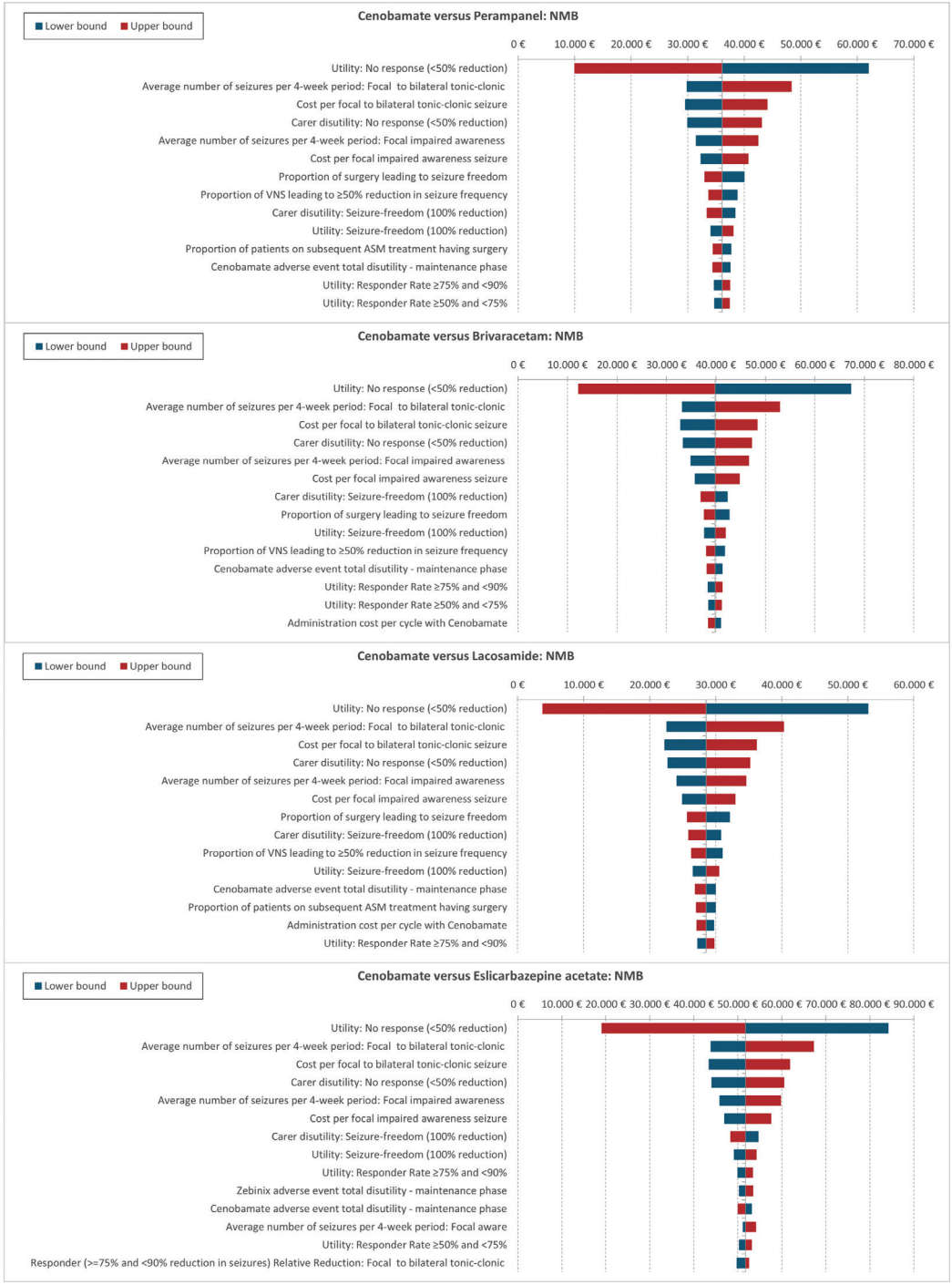

FIGURE 2 - Tornado diagram.

essential to determine the economic sustainability of new drugs and therapies, ensure the efficient use of healthcare resources, and guarantee that patients receive the best possible care without placing excessive burdens on healthcare systems. Analyzing the cost-effectiveness of various treatments can help policymakers make more informed decisions and optimize the allocation of public and private funds for epilepsy management.

Previous studies have demonstrated the clinical benefits of cenobamate compared to other third-generation ASMs, showing how it leads to reduced healthcare resource utilization, particularly in terms of fewer specialist visits and emergency department admissions (32,61,62).

Cenobamate's efficacy has been studied and proven across all types of focal seizures, including bilateral tonic-clonic seizures, which are associated with an increased risk of morbidity and mortality (63,64). This results in a reduced need for medical care, hospitalization, and pharmacological treatments, as well as a lower social and psychological burden for patients and their caregivers.

FIGURE 3 - Cost-effectiveness plane and acceptability curve.

This study also revealed that reducing and controlling seizures leads to a lower total cost for cenobamate compared to the alternative treatments due to the reduction in other cost components contributing to the overall expenditure per patient. Cenobamate was associated with a per-patient cost of €151,794.72, compared to €167,751.43 for lacosamide, €174,221.54 for perampanel, €177,385.43 for brivaracetam and €184,492.60 for eslicarbazepine acetate, making it dominant over all the alternatives considered.

Specifically, cenobamate was associated with lower costs related to seizure management, totaling €110,600.42, compared to €144,736.70 for brivaracetam, €141,251.65 for lacosamide, €142,588.62 for perampanel and €151,045.08 for eslicarbazepine acetate.

The relationship between the clinical and economic benefits of cenobamate compared to third-generation ASMs has been analyzed in other studies, which highlighted the incremental benefit of cenobamate over these ASMs (28,65-68).

Notably, the study by Villanueva et al. (68) found that cenobamate had the lowest values at all doses for both the ≥50% response rate and seizure freedom compared to the alternatives. In terms of costs per ≥50% response rate, cenobamate was associated with the lowest values at the defined daily dose (DDD), while lacosamide and eslicarbazepine acetate had the lowest values at their minimum and maximum doses, respectively.

In our study, treatment with cenobamate was associated with 7.54 QALYs and total costs of €151,794.72 per patient, consistent with the findings of Laskier et al. (28), where cenobamate was dominant over all comparators, with the lowest cost and the highest QALY gain compared to other third-generation ASM therapies. Compared to the cited study, which estimated the cost-effectiveness of cenobamate in the UK context, the sources used for efficacy data were the same except for RR and odds ratios used to estimate the effectiveness and incidence of adverse events for the comparators.

Moreover, the use of cenobamate has been shown to have positive effects on the quality of life, an area that is significantly compromised in people with epilepsy (68). Studies examining this aspect have reported a marked improvement in QoL resulting from the use of cenobamate (69,70).

In this study, cenobamate's total QALYs were 7.54, compared to 6.91 for lacosamide, 6.85 for perampanel, 6.82 for brivaracetam, and 6.58 for eslicarbazepine acetate.

Cenobamate emerges as a particularly advantageous therapy, not only for reducing the number of seizures and associated burden but also for lowering overall management costs, proving to be dominant compared to alternative therapies.

However, the study's results should be interpreted in the context of certain limitations. One limitation is the lack of published data on alternative treatments and resource use, with most data obtained through input from clinical experts. Also, a potential limitation is that the extrapolation of long-term treatment discontinuation is based on a generalized gamma parametric distribution, which, despite being supported by clinical opinion and statistical criteria, may not fully capture real-world treatment persistence. A further limitation concerns the estimated cost of adverse events, which may be underestimated since the cost of a specialist visit has been assumed for all events. However, as the degree of adverse events is not known, this approach was found to be the most conservative in order to provide an estimate of the cost associated with adverse events. Another limitation is the absence of head-to-head comparative data between the considered therapeutic alternatives. In this regard, indirect comparisons were necessary using a NMA. Despite the uncertainty surrounding the long-term efficacy and safety of cenobamate and its comparators, due to the lack of direct comparative studies, NMA offers the opportunity to synthesize evidence from clinical trials and compare treatments that have not been directly assessed in single studies.

Finally, with the aim of conducting a direct comparison between cenobamate and the most innovative and widely used therapies in clinical practice, older-generation ASMs were excluded from the analysis.

Conclusion

The cost-effectiveness analysis demonstrated that cenobamate is a more effective therapeutic alternative than brivaracetam, lacosamide, eslicarbazepine acetate, and perampanel for the treatment of FOS. Despite a slight increase in acquisition costs, treatment with cenobamate generates significant cost offsets and improves the quality of life due to better seizure control and increased quality-adjusted life expectancy. The improvement in quality of life is reflected in higher response rates (seizure reduction >50%) and remission rates (patients achieving 100% seizure reduction) compared to the analyzed alternatives. The cost-effectiveness analysis shows that cenobamate is dominant over all the alternatives evaluated.

Disclosures

Conflict of interest: The authors declare that they have no conflicts of interest.

Financial Support: This study was funded by Angelini Pharma S.p.a.

References

1. World Health Organization. "Epilepsy: a public health imperative" Online (Accessed October 2024)
2. Mesraoua B, Deleu D, Hassan AH, et al. Dramatic outcomes in epilepsy: depression, suicide, injuries, and mortality. Curr Med Res Opin. 2020;36(9):1473-1480. CrossRef PubMed
3. Beghi E. The epidemiology of epilepsy. Neuroepidemiology. 2020;54(2):185-191. CrossRef PubMed
4. Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. Neurology. 2017;88(3):296-303. CrossRef PubMed
5. Baulac M, de Boer H, Elger C, et al. Epilepsy priorities in Europe: a report of the ILAE-IBE Epilepsy Advocacy Europe Task Force. Epilepsia. 2015;56(11):1687-1695. CrossRef PubMed
6. Mennini FS. The potential impact of PNNR on the management of patients with epilepsy. Global & Regional Health Technology Assessment. 2022;9(Suppl 2):1–3. CrossRef.
7. Giussani G, Cricelli C, Mazzoleni F, et al. Prevalence and incidence of epilepsy in Italy based on a nationwide database. Neuroepidemiology. 2014;43(3-4):228-232. CrossRef PubMed

8. Zaccara G, Citerio G, Del Gaudio A, et al. Clinical pathways of epileptic seizures and status epilepticus: results from a survey in Italy. Neurol Sci. 2020;41(6):1571-1575. CrossRef PubMed
9. Giussani G, Franchi C, Messina P, et al. Prevalence and incidence of epilepsy in a well-defined population of Northern Italy. Epilepsia. 2014;55(10):1526-1533. CrossRef PubMed
10. Gaitatzis A, Sisodiya SM, Sander JW. The somatic comorbidity of epilepsy: a weighty but often unrecognized burden. Epilepsia. 2012;53(8):1282-1293. CrossRef PubMed
11. Keezer MR, Sisodiya SM, Sander JW. Comorbidities of epilepsy: current concepts and future perspectives. Lancet Neurol. 2016;15(1):106-115. CrossRef PubMed
12. Fisher RS. The new classification of seizures by the International League against Epilepsy 2017. Curr Neurol Neurosci Rep. 2017;17(6):48. CrossRef PubMed
13. Wirrell EC, Grossardt BR, Wong-Kisiel LCL, et al. Incidence and classification of new-onset epilepsy and epilepsy syndromes in children in Olmsted County, Minnesota from 1980 to 2004: a population-based study. Epilepsy Res. 2011;95(1-2):110-118. CrossRef PubMed
14. Gupta S, Ryvlin P, Faught E, et al. Understanding the burden of focal epilepsy as a function of seizure frequency in the United States, Europe, and Brazil. Epilepsia Open. 2017;2(2):199-213. CrossRef PubMed
15. Chen Z, Brodie MJ, Liew D, et al. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. JAMA Neurol. 2018;75(3):279-286. CrossRef PubMed
16. Kalilani L, Sun X, Pelgrims B, et al. The epidemiology of drug-resistant epilepsy: A systematic review and meta-analysis. Epilepsia. 2018;59(12):2179-2193. CrossRef PubMed
17. Picot MC, Baldy-Moulinier M, Daurès JP, et al. The prevalence of epilepsy and pharmacoresistant epilepsy in adults: a population-based study in a Western European country. Epilepsia. 2008;49(7):1230-1238. CrossRef PubMed
18. Krauss GL, Klein P, Brandt C, et al. Safety and efficacy of adjunctive cenobamate (YKP3089) in patients with uncontrolled focal seizures: a multicentre, double-blind, randomized, placebo-controlled, dose-response trial. Lancet Neurol. 2020;19(1):38-48. CrossRef PubMed
19. Chung SS, French JA, Kowalski J, et al. Randomized phase 2 study of adjunctive cenobamate in patients with uncontrolled focal seizures. Neurology. 2020;94(22):e2311-e2322. CrossRef PubMed
20. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010;51(6):1069-1077. CrossRef PubMed
21. Laxer KD, Trinka E, Hirsch LJ, et al. The consequences of refractory epilepsy and its treatment. Epilepsy Behav. 2014;37:59-70. CrossRef PubMed
22. Mecarelli O, Di Gennaro G, Vigevano F. Unmet needs and perspectives in management of drug resistant focal epilepsy: an Italian study. Epilepsy Behav. 2022;137(Pt A):108950. CrossRef PubMed
23. Silva B, Canas-Simião H, Cordeiro S, et al. Determinants of quality of life in patients with drug-resistant focal epilepsy. Epilepsy Behav. 2019;100(Pt A):106525. CrossRef PubMed
24. Luoni C, Canevini MP, Capovilla G, et al. A prospective study of direct medical costs in a large cohort of consecutively enrolled patients with refractory epilepsy in Italy. Epilepsia. 2015;56(7):1162-1173. CrossRef PubMed
25. Allers K, Essue BM, Hackett ML, et al. The economic impact of epilepsy: a systematic review. BMC Neurol. 2015;15(1):245. CrossRef PubMed
26. Osservatorio Nazionale sull'impiego dei Medicinali. L'uso dei farmaci in Italia. Rapporto Nazionale 2015. Osmed. Online (Accessed October 2024)
27. Laskier V, Agyei-Kyerematen KK, Eddy AE, et al. Cost-effectiveness of cenobamate for focal seizures in people with drug-resistant epilepsy. Epilepsia. 2023;64(4):843-856. CrossRef PubMed
28. Husereau D, Drummond M, Petrou S, et al. ISPOR Health Economic Evaluation Publication Guidelines-CHEERS Good Reporting Practices Task Force. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—explanation and elaboration: a report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. Value Health. 2013;16(2):231-250. CrossRef PubMed
29. French JA, Chung SS, Krauss GL, et al. Long-term safety of adjunctive cenobamate in patients with uncontrolled focal seizures: open-label extension of a randomized clinical study. Epilepsia. 2021;62(9):2142-2150. CrossRef PubMed
30. Associazione Italiana Economia Sanitaria (AIES), Proposta di Linee-Guida per la valutazione economica degli interventi sanitari. Politiche Sanitarie. 2009;10(2):91-99. Online
31. Mulheron S, Leahy TP, McStravick M, Doran R, Delanty N. A comparison of cenobamate with other newer anti-seizure medications for adjunctive treatment of focal-onset seizures: A systematic review and network meta-analysis. Seizure. 2024;118:80-90. CrossRef PubMed
32. Sperling MR, Klein P, Aboumatar S, et al. Cenobamate (YKP3089) as adjunctive treatment for uncontrolled focal seizures in a large, phase 3, multicenter, open-label safety study. Epilepsia. 2020;61(6):1099-1108. CrossRef PubMed
33. O'Brien TJ, Borghs S, He QJ, et al. Long-term safety, efficacy, and quality of life outcomes with adjunctive brivaracetam treatment at individualized doses in patients with epilepsy: an up to 11-year, open-label, follow-up trial. Epilepsia. 2020;61(4):636-646. CrossRef PubMed
34. Rosenfeld W, Fountain NB, Kaubrys G, et al.; SP615 Study Investigators. Safety and efficacy of adjunctive lacosamide among patients with partial-onset seizures in a long-term open-label extension trial of up to 8 years. Epilepsy Behav. 2014;41:164-170. CrossRef PubMed
35. Hufnagel A, Ben-Menachem E, Gabbai AA, et al. Long-term safety and efficacy of eslicarbazepine acetate as adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy: results of a 1-year open-label extension study. Epilepsy Res. 2013;103(2-3):262-269. CrossRef PubMed
36. Halász P, Cramer JA, Hodoba D, et al. BIA-2093-301 Study Group. Long-term efficacy and safety of eslicarbazepine acetate: results of a 1-year open-label extension study in partial-onset seizures in adults with epilepsy. Epilepsia. 2010 Oct;51(10):1963-9 CrossRef
37. Krauss GL, Perucca E, Kwan P, et al. Final safety, tolerability, and seizure outcomes in patients with focal epilepsy treated with adjunctive perampanel for up to 4 years in an open-label extension of phase III randomized trials: Study 307. Epilepsia. 2018;59(4):866-876. CrossRef PubMed
38. Picot MC, Jaussent A, Neveu D, et al. Cost-effectiveness analysis of epilepsy surgery in a controlled cohort of adult patients with intractable partial epilepsy: a 5-year follow-up study. Epilepsia. 2016;57(10):1669-1679. CrossRef PubMed
39. Hamilton P, Soryal I, Dhahri P, et al. Clinical outcomes of VNS therapy with AspireSR® (including cardiac-based seizure detection) at a large complex epilepsy and surgery centre. Seizure. 2018;58:120-126. CrossRef PubMed
40. Sperling MR, Barshow S, Nei M, Asadi-Pooya AA. A reappraisal of mortality after epilepsy surgery. Neurology. 2016;86(21):1938-1944. CrossRef PubMed

41. Granbichler CA, Nashef L, Selway R, et al. Mortality and SUDEP in epilepsy patients treated with vagus nerve stimulation. Epilepsia. 2015;56(2):291-296. CrossRef PubMed
42. Istituto Nazionale di Statistica (ISTAT). Tavole di mortalità della popolazione residente. Online (Accessed October 2024)
43. Trinka E, Bauer G, Oberaigner W, et al. Cause-specific mortality among patients with epilepsy: results from a 30-year cohort study. Epilepsia. 2013;54(3):495-501. CrossRef PubMed
44. Archivio Farmadati. Online (Accessed October 2024)
45. Agenzia Europea dei Medicinali (EMA). Riassunto caratteristiche del prodotto. Ontozry Online (Accessed October 2024)
46. WHO Collaborating Centre for Drug Statistics Methodology (WHOCC). Defined Daily Dose (DDD). Online: (Accessed October 2024)
47. Agenzia Europea dei Medicinali (EMA). Riassunto caratteristiche del prodotto. Zebinix. Online (Accessed October 2024)
48. Agenzia Europea dei Medicinali (EMA). Riassunto caratteristiche del prodotto. Vimpat. Online (Accessed October 2024)
49. Agenzia Europea dei Medicinali (EMA). Riassunto caratteristiche del prodotto. Nubriveo. Online (Accessed October 2024)
50. Agenzia Europea dei Medicinali (EMA). Riassunto caratteristiche del prodotto. Fycompa. Online (Accessed October 2024)
51. Ministero della Salute. Decreto tariffe del 23 giugno 2023. Online (Accessed October 2024)
52. Ministero dell'Economia e delle Finanze. Conto annuale della ragioneria dello Stato 2021. Online (Accessed October 2024)
53. Tariffario nazionale. Remunerazione delle prestazioni di assistenza ospedaliera. Online (Accessed October 2024)
54. Ministero della Salute. Rapporto annuale sull'attività di ricovero ospedaliero (Dati SDO 2020). Online (Accessed October 2024)
55. Briggs A, Claxton K, Sculpher M. Decision modelling for health economic evaluation. 2006. CrossRef.
56. Hader WJ, Tellez-Zenteno J, Metcalfe A, et al. Complications of epilepsy surgery: a systematic review of focal surgical resections and invasive EEG monitoring. Epilepsia. 2013;54(5):840-847. CrossRef PubMed
57. M. Panebianco, A. Rigby, J. Weston, and A. G. Marson. Vagus nerve stimulation for partial seizures. 2015, Issue 4 CrossRef.
58. Flint I, Medjedovic J, Drogon O'Flaherty E, et al. Mapping analysis to predict SF-6D utilities from health outcomes in people with focal epilepsy. Eur J Health Econ. 2023;24(7):1061-1072. CrossRef PubMed
59. de Kinderen RJA, Wijnen BF, van Breukelen G, et al. From clinically relevant outcome measures to quality of life in epilepsy: A time trade-off study. Epilepsy Res. 2016;125:24-31. CrossRef PubMed
60. Lattanzi S, Trinka E, Zaccara G, et al. Third-generation antiseizure medications for adjunctive treatment of focal-onset seizures in adults: a systematic review and network meta-analysis. Drugs. 2022;82(2):199-218. CrossRef PubMed
61. Privitera M, Richy FF, Schabert VF. Indirect treatment comparison of cenobamate to other ASMs for the treatment of uncontrolled focal seizures. Epilepsy Behav. 2022;126:108429. CrossRef PubMed
62. Whitney R, Donner EJ. Risk factors for sudden unexpected death in epilepsy (SUDEP) and their mitigation. Curr Treat Options Neurol. 2019;21(2):7. CrossRef PubMed
63. Harden C, Tomson T, Gloss D, et al. Practice guideline summary: sudden unexpected death in epilepsy incidence rates and risk factors: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2017;88(17):1674-1680. CrossRef PubMed
64. Ángel Calleja M, Navarro A, Serratosa JM, et al. Determination of the economically justifiable price of cenobamate in the treatment of focal-onset seizures in adult patients with drug-resistant epilepsy in Spain. Expert Rev Pharmacoecon Outcomes Res. 2022;22(7):1127-1136. CrossRef PubMed
65. Villanueva V, Serratosa JM, Toledo M, et al. Number needed to treat and associated cost analysis of cenobamate versus third-generation anti-seizure medications for the treatment of focal-onset seizures in patients with drug-resistant epilepsy in Spain. Epilepsy Behav. 2023;139:109054. CrossRef PubMed
66. NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE - SINGLE TECHNOLOGY APPRAISAL. Cenobamate for focal onset seizures in epilepsy. 2021. Online (Accessed October 2024)
67. Ioannou P, Foster DL, Sander JW, et al. The burden of epilepsy and unmet need in people with focal seizures. Brain Behav. 2022;12(9):e2589. CrossRef PubMed
68. Elizebath R, Zhang E, Coe P, et al. Cenobamate treatment of focal-onset seizures: quality of life and outcome during up to eight years of treatment. Epilepsy Behav. 2021;116:107796. CrossRef PubMed
69. Catalán-Aguilar J, Hampel KG, Cano-López I, et al. Prospective study of cenobamate on cognition, affectivity, and quality of life in focal epilepsy. Epilepsia Open. 2024;9(1):223-235. CrossRef PubMed
70. Oppong R, Kaambwa B, Nuttall J, et al. The impact of using different tariffs to value EQ-5D health state descriptions: an example from a study of acute cough/lower respiratory tract infections in seven countries. Eur J Health Econ. 2013;14(2):197-209. CrossRef PubMed
71. Matza LS, Deger KA, Vo P, et al. Health state utilities associated with attributes of migraine preventive treatments based on patient and general population preferences. Qual Life Res. 2019;28(9):2359-2372. CrossRef PubMed
72. Mangen MJJ, Huijts SM, Bonten MJM, et al. The impact of community-acquired pneumonia on the health-related quality-of-life in elderly. BMC Infect Dis. 2017;17(1):208. CrossRef PubMed
73. McGill F, Griffiths MJ, Bonnett LJ, et al. Incidence, aetiology, and sequelae of viral meningitis in UK adults: a multicentre prospective observational cohort study. Lancet Infect Dis. 2018;18(9):992-1003. CrossRef PubMed
74. Chotai S, Parker SL, Sivaganesan A, et al. Effect of complications within 90 days on patient-reported outcomes 3 months and 12 months following elective surgery for lumbar degenerative disease. Neurosurg Focus. 2015;39(6):E8. CrossRef PubMed
75. Utne KK, Tavoly M, Wik HS, et al. Health-related quality of life after deep vein thrombosis. Springerplus. 2016;5(1):1278. CrossRef PubMed