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Budget impact analysis of cenobamate, a novel adjunctive therapy for the treatment of drug resistant focal onset seizures, from the Belgian healthcare payer perspective

Kristl Vonck[a], Olivier Bodart[b], Sarah Weckhuysen[c], Ann Tanghe[d], Britt Callebaut[d], Caroline Verdonck[d], Lynn Van den Bergh[e] and Benjamin Legros[f]

[a]Department Neurology – 4Brain, Ghent University Hospital, Ghent, Belgium; [b]Neurology Department, University Hospital of Liège, Liège, Belgium; [c]Neurology Department, University Hospital Antwerp, Antwerp, Belgium; [d]Hict NV, Ghent, Belgium; [e]Angelini Pharma, Paris, France; [f]Neurology Department, HUB-Hôpital Erasme, Brussels, Belgium

ABSTRACT

Objective: Cenobamate has recently been introduced as new anti-seizure medication (ASM) for patients with focal onset seizures (FOS) who are insufficiently controlled despite the use of three previous ASMs. To date, few evaluations have addressed the budgetary impact for the healthcare payer of add-on ASMs in patients with drug-resistant epilepsy (DRE). This study aims to assess the budgetary implications for the Belgian health insurer, the National Institute for Health and Disability Insurance (NIHDI), if cenobamate were reimbursed for the adjuvant treatment of FOS in adults with DRE.

Methods: A prevalence-based budget impact model (BIM) was developed from the perspective of the Belgian NIHDI, considering all direct healthcare costs over a 3-year time horizon. A standardized expert elicitation process with experienced epileptologists was conducted to collect data on Belgian clinical practice. Source data uncertainty impact was investigated through a one-way sensitivity analysis (OWSA).

Results: Over a 3-year period, considering the cumulative drug costs of cenobamate, replacement of other third-generation ASMs, and savings generated at medical cost level, the introduction of cenobamate as adjunctive treatment for the target population was estimated to reduce the NIHDI budget by −€8,105,616. The robustness of these savings was confirmed through an OWSA.

Conclusion: The savings at medical cost level fully offset the impact of cenobamate on the drug budget, leading to an overall healthcare budget saving of −€8,105,616 for NIHDI. This favourable outcome is largely due to cenobamate's high efficacy reflected in its high response rate and significant effect on reducing seizure frequency.

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Introduction

In Belgium, ∼ 47,000 adult patients are estimated to suffer from focal onset seizures (FOS)[1–3], seizures originating from a localized region in one hemisphere of the brain region due to abnormal electrochemical activity. In general, FOS patients are treated with anti-seizure medication (ASM); achieving seizure freedom is the primary goal of treatment[4]. Treatment of FOS typically starts with ASM monotherapy. If monotherapy proves ineffective, a second ASM is introduced either as a substitute (preferably) or add-on therapy. If this second ASM also fails, the patient is classified to have drug resistant epilepsy (DRE). DRE is defined as the failure of two adequately trialled and tolerated ASM regimens to achieve sustained seizure freedom. In this case, further trials with various ASM combinations are required, or non-ASM treatment options can be considered, including brain surgery and neurostimulation techniques like vagus nerve stimulation (VNS) or deep brain stimulation (DBS). As a result, there is an ongoing need for the development of novel ASMs. Cenobamate, a novel ASM, is indicated as adjunctive treatment for FOS in adult patients with DRE. Consistent with Belgian reimbursement criteria of

CONTACT Caroline Verdonck caroline.verdonck@hict.be Hict NV, Poortakkerstraat 93, 9051 Ghent, Belgium
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other fourth line treatments (lacosamide, brivaracetam, and perampanel), cenobamate is reimbursed for patients who have failed at least three previous ASM therapies. In the Netherlands, the introduction of cenobamate was estimated to be cost saving from a societal perspective, mainly due to a decrease in productivity costs and acute event management costs[5]. In Belgium, healthcare costs are paid largely by the National Institute for Health and Disability Insurance (NIHDI), with varying patient shares per healthcare resource. As a result of changing demographics and increasing healthcare costs, the NIHDI budget is under serious strain, requiring rational decision-making when it comes to drug reimbursement. From the Belgian NIHDI perspective, productivity costs are not considered in decision making while the total impact on all direct healthcare resource use is essential. Therefore, this budget impact analysis sought to evaluate the overall financial implications for the Belgian NIHDI, if cenobamate is reimbursed for the add-on treatment of FOS adult patients with epilepsy, who have not been adequately controlled despite a history of treatment with at least three ASMs. This analysis is unique in that it comprehensively assesses the total cost impact at all levels when introducing a new product to clinical practice.

Materials and methods

Model framework

A prevalence-based budget impact model (BIM) was developed in Excel that follows the prevalent cases of adult epilepsy patients with FOS in Belgium over a 3-year time horizon, in accordance with both national[6] and international guidelines[7].

Model calculations

The model calculates the incremental budget impact on the total NIHDI budget consequential to the reimbursement of cenobamate for DRE patients with FOS who failed at least three previous ASMs. The incremental budget impact is the difference between total NIHDI budget expenditures with cenobamate reimbursement and the expenditures of the clinical practice before cenobamate was reimbursed.

The calculation of the budget expenditure consists of two main components. First, the population size is determined and distributed across the different treatment options and phases, over a time horizon of 3 years, based on market shares. Second, costs are calculated and assigned to each treatment option and phase. The total cost is obtained by multiplying treatment costs (second part) with the corresponding number of patients (first part). Figure 1 provides an overview of the model structure.

All costs and results are presented according to three levels: drug budget (ASMs only), medical cost budget (drug administration, disease monitoring, seizure treatment and AEs), and total healthcare budget (combining drug and medical cost budget) over a 3-year time horizon. Costs are determined by combining unit costs with resource utilization, supplemented by clinical data related to response rates and seizure frequency.

To assess the impact of uncertainty in the input data on the budget impact analysis, a one-way sensitivity analysis (OWSA) was conducted, in which relevant model parameters were varied by 30% (i.e. a 30% increase or decrease of the base case value).

Model inputs

The model calculates the budget impact from the perspective of the NIHDI, taking into account all potential direct healthcare costs. This includes costs from drug acquisition, drug administration, disease monitoring, management of adverse events (AEs) and treatment of different seizure types known to present in patients with FOS (both outpatient and inpatient costs).

Model inputs required are the eligible patient population, market shares of cenobamate and comparator treatments in a world with and without cenobamate, clinical input data (baseline seizure frequency; treatment response, cenobamate dosing, AE probability and clinical practice) (Table 1) and cost inputs. Data on the eligible patient population, market shares and resource use were obtained by application of a structured expert elicitation process (AT, BC) with three Belgian epileptologists experienced in treating DRE patients with FOS (including KV and BJ). During this process, each expert was independently asked to complete a questionnaire. For each of the required inputs, the questionnaire asked the experts to validate proposed inputs derived from literature (e.g. to validate the most relevant input source for determining the adult epileptic population from four Belgian scientific sources) or, if literature for Belgium was unavailable, validate a foreign source or provide alternative inputs. After the survey, individual interviews with each expert took place for further elicitation. Afterwards, final survey answers were processed to calculate median/mean values.

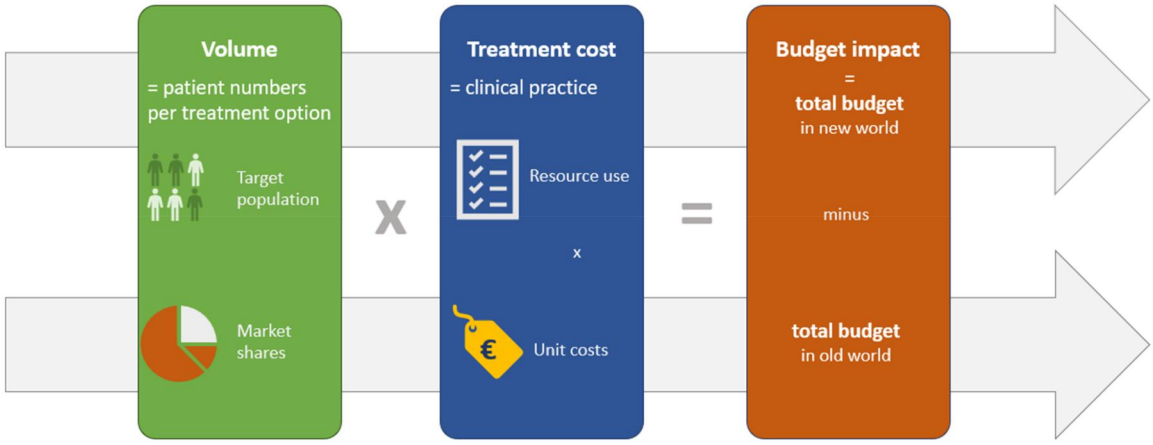

Figure 1. Model structure.

Table 1. Clinical and resource use inputs used in the model.

Clinical inputs		
Baseline seizure frequency in patients with drug-resistant FOS		
Focal aware seizures/4 weeks	4.63	UK expert opinion – validated by Belgian experts[3,5,15]
Focal seizures with impaired awareness/4 weeks	6.25	UK expert opinion – validated by Belgian experts[3,5,15]
Focal seizures generalizing to bilateral tonic-clonic seizures/4 weeks	2.50	UK expert opinion – validated by Belgian experts[3,5,15]
Treatment response		
Response rate ≥ 50% seizure frequency reduction (placebo)	25%	Krauss et al.[18]
≥50% seizure frequency reduction compared to placebo (OR)		
Perampanel	1.46	NMA[17]
Brivaracetam	1.54	NMA[17]
Lacosamide	2.07	NMA[17]
Cenobamate	3.77	NMA[17]
Response rate for seizure freedom (placebo)	1%	Krauss et al.[18]
Seizure freedom compared to placebo (OR)		
Perampanel	4.45	NMA[17]
Brivaracetam	6.75	NMA[17]
Lacosamide	3.85	NMA[17]
Cenobamate	12.62	NMA[17]
Treatment dosing		
Perampanel (DDD)	8 mg	[42]
Brivaracetam (DDD)	100 mg	[43]
Lacosamide (DDD)	300 mg	[44]
Cenobamate dosing (average daily dose)	215.1 mg	C021 study[23]
AE probability		
Incidence of TEAE for cenobamate during titration phase		
Somnolence	22.0%	[5,23]
Dizziness	16.6%	[5,23]
Headache	7.5%	[5,23]
Fatigue	12.9%	[5,23]
Incidence of TEAE for cenobamate during maintenance phase		
Somnolence	5.1%	[5,23]
Dizziness	8.1%	[5,23]
Headache	5.4%	[5,23]
Resource use		
Resource use for routine monitoring per response type	Supplementary Materials	Expert elicitation[3]
Resource use for the management of acute events per seizure type	Supplementary Materials	UK expert opinion[15] – validated by Belgian experts[3]
Resource use for the management of TEAEs	Supplementary Materials	Campone et al. 2014[27]
% of focal aware seizures needing medical attention	2.9%	Expert elicitation[3]
% of focal seizures with impaired awareness needing medical attention	10.0%	Expert elicitation[3]
% of focal seizures generalizing to bilateral tonic-clonic seizures	40.0%	Expert elicitation[3]

Abbreviations: OR, odds ratio; TEAE, treatment-emergend adverse events; UK, United Kingdom.

Eligible patient population

The eligible patient population was calculated using real-world data on the Belgian population[8,9] and literature on prevalence, incidence, and treatment response to previous treatments[1,2,10–12]. In the first year of the model (November 2022–October 2023), the adult population in Belgium consisted of 9,206,128 adults[8]. The model accounts for an annual population growth of 0.54%[8] and a mortality rate of 0.9162%[13].

The epilepsy prevalence in Belgian adults is 0.9%[1,3]. Among patients with epilepsy, approximately 57% have FOS[1–3,10,12], resulting in just over 47,000 adult FOS patients in Belgium. Of these, approximately 38.2% have insufficiently controlled disease with first line monotherapy, and move to a second ASM[3,11]. Of the patients that switched to or added a second ASM, approximately 58.3% failed to respond sufficiently to the second ASM therapy[3,11]. Thereafter, the DRE-patient population will either start a third ASM therapy (95%), or switch to VNS (2.5%) or surgery (2.5%)[3]. The latter two fail in, respectively, 72.8% and 36.1% of cases[3], after which patients still end up proceeding to a third-line ASM therapy[3]. Among these patients, regardless of their previous treatment history, 83.4% are expected to maintain insufficient control over their disease[3,11]. This results in an eligible patient population of 8572 patients for fourth line treatment (with ASMs) in the first year of the model (Figure 2).

Market shares and comparators

The number of patients per treatment option depends on the market shares for each of the options available. The market shares of the different treatment options in both current and future clinical practice (without and including cenobamate, respectively) were determined based on real-world sales data[14] and expert opinion[3]. In a world with cenobamate, it was estimated that in the first year of the model, 514 patients would be treated with cenobamate. This population would grow to 1733 patients in the third year of the model. Comparator treatments (= alternatives to cenobamate) were identified as perampanel, brivaracetam, and lacosamide. While other treatments exist that can be used in drug-resistant FOS, these are not included in the comparison as they generate more side-effects and adverse events (AEs) compared to perampanel, brivaracetam and lacosamide, which are third-generation (= newer) treatments. Together with cenobamate, perampanel, brivaracetam, and lacosamide are the only four third-generation ASMs that are reimbursed in Belgium for the treatment of drug-resistant FOS. The choice of comparators was validated by the Belgian epileptologists[3]. In addition, non-ASM options (VNS, surgery, and inclusion in clinical trials) were included in the comparison, and market shares applied. A detailed overview of the estimated patient numbers per treatment option, both in a world with and without cenobamate, is provided in the Supplementary Materials.

Clinical inputs

Clinical inputs consist of baseline seizure frequency, treatment response (proportion of patients responding and seizure frequency reduction per response type), cenobamate dosing, and AE probability.

Baseline seizure frequency. Baseline seizure frequency for focal aware seizures, focal seizures with impaired awareness, and focal seizures generalizing to bilateral tonic-clonic seizures in the eligible patient population were retrieved from a UK expert opinion, and validated by Belgian experts[3], to be 4.63, 6.25, and 2.5 per 4 weeks, respectively. These values were also used in Laskier et al.[15] and Li et al.[5]

Treatment response. Treatment response was calculated based on the average reduction in seizure frequency per response type[16] and the proportion of patients responding to treatment per treatment[17,18].

Data on the average seizure frequency reduction per seizure type and response category were generated from the C017 study using patient-level data[16] and shown in Table 2. These data were also used in Laskier et al.[15] and Li et al.[5] Together with the proportions of patients responding to treatment, per treatment, this informs the individual treatment efficacy of perampanel, brivaracetam, lacosamide and cenobamate.

The proportion of patients responding to treatment was derived from a network meta-analysis (NMA)[17] published by the National Institute for Health and Care Excellence (NICE) as part of the NICE guideline NG217[19], and proportions of patients responding to placebo derived from Krauss et al.[18] The choice of this NMA – compared to the NMA used in the budget impact analysis of Li et al.[5], conducted by Laskier et al.[15] – is based on the fact that it has been published by NICE[19], and on its more conservative results regarding the proportion of patients in the high, very high, and complete response categories for cenobamate.

The reported estimated odds ratios (ORs) for achieving $\geq$50% reduction in seizure frequency for FOS compared to placebo were 1.46, 1.54, 2.07, and

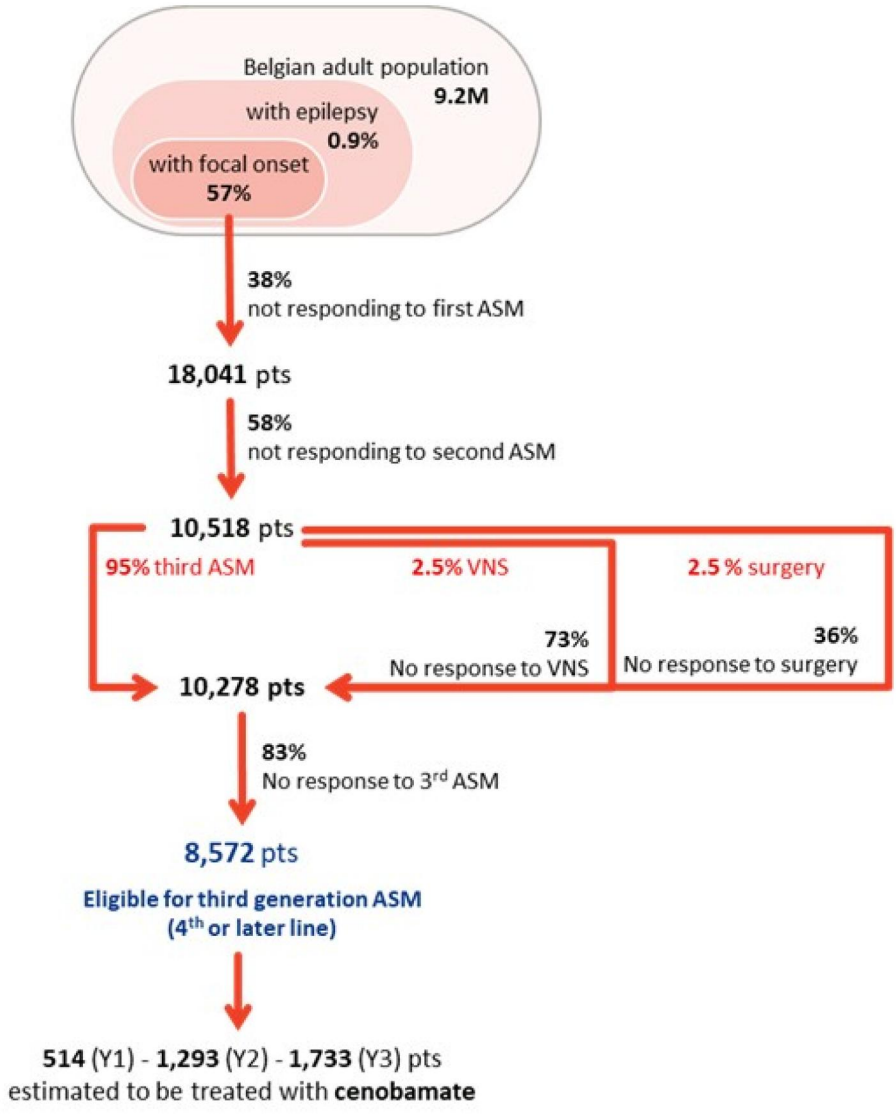

Figure 2. Eligible patient population.
Abbreviations: ASM, Anti-seizure medication; VNS, Vagus nerve stimulation.

Table 2. Seizure frequency at baseline and average reduction per seizure type.

Type of response	Focal aware	Focal impaired aware	Focal to bilateral tonic-clonic
Baseline seizure frequency[3,5,15]			
Average number of seizures per 4 weeks	4.63	6.25	2.50
Average reduction in seizures by response category[5,15,16]			
No response	−18.6%	−7.1%	7.1%
Moderate response	68.3%	59.7%	60.8%
High response	80.5%	84.3%	83.1%
Very high response	96.0%	95.5%	95.1%
Complete response	100.0%	100.0%	100.0%

3.77 for perampanel, brivaracetam, lacosamide, and cenobamate, respectively[17]. For seizure freedom, the reported ORs were 4.45, 6.75, 3.85, and 12.62, respectively[17]. In the model, the OR for ≥50% seizure frequency reduction was applied across moderate, high, and very high response states, in line with Li et al.[5], Laskier et al.[15], and Paoletti et al.[20] These ORs were converted to relative risk (RRs) versus placebo, based on the following formula:

$$RR = OR/(1\text{-}p + (p * OR));$$

with p being the risk of the control group.

To calculate the proportion of patients responding to treatment per product and per response category,

Table 3. Proportion of patients responding to treatment – per therapy.

Type of response	Description	Placebo[18]	Perampanel	Brivaracetam	Lacosamide	Cenobamate
No response	Uncontrolled epilepsy, less than 50% reduction in seizures after addition of adjunctive treatment	74.5%	63.7%	60.5%	56.3%	34.3%
Moderate response	50–75% reduction in seizure rate following addition of adjunctive treatment	15.7%	20.5%	21.3%	25.6%	34.9%
High response	75–90% reduction in seizures after addition of adjunctive treatment	6.9%	9.0%	9.3%	11.2%	15.3%
Very high response	90–100% reduction in seizures after the addition of adjunctive treatment	2.0%	2.6%	2.7%	3.2%	4.4%
Complete response	Seizure freedom – 100% reduction in seizures	1.0%	4.2%	6.3%	3.7%	11.1%

Response for treatments = response placebo[18] × risk ratios (calculated based on OR as reported by NICE[17]).

the product-specific RR was multiplied by the proportion of patients responding to placebo; using a placebo response rate of 25% for ≥50% reduction and 1% for seizure freedom, based on Krauss et al.[18] The calculated proportions of patients responding to treatment, per treatment, and per response category, is provided in Table 3.

These response rates inform the model's monitoring costs as monitoring of patients depends on the response they have on their treatment. Additionally, response rates drive average seizure[21,22] (reduction = lower costs to treat seizures).

Treatment dosing. Although the defined daily dose (DDD) for cenobamate is 200 mg per day, the dosages given in the 200 mg and 400 mg treatment arms of the C021 study[23] were used in the model to better align with actual cenobamate dosing. An average maintenance dose of 215.1 mg per day was calculated.

Drug usage for the comparator therapies was based on the dosing regime in the Summary of Product Characteristics (SPC), complemented with DDD data[24], guidelines[12], and expert opinion[3]. For cenobamate, lacosamide, and perampanel, a titration phase was taken into account in which treatment dosing was gradually increased in line with guidelines and SPCs of the products[21,25,26], which allows to make a distinction in the drug costs between the initiation year and maintenance years per treatment option, and to account for variable titration phases between ASMs.

In the base case, drug wastage was factored in. While it was assumed that patients who initiated treatment would remain on it for the model's entire time horizon, the model also accounted for treatment discontinuation by considering incidence, prevalence, and mortality.

AE probability. The AE probabilities for cenobamate were based on the reported incidence of treatment-emergent adverse events (TEAE) in the titration phase and maintenance phase[5,23]. Only TEAEs occurring in more than 5% of patients receiving cenobamate were included in the model, more specifically somnolence, dizziness, headache, and fatigue. For other ASMs, AE incidence was assumed to be equal to the AE incidence in cenobamate, as the NICE[17] was unable to conduct an NMA for AEs due to inconsistencies in or non-reporting of AE outcomes across different trials. No AEs were assumed for surgery or VNS.

Cost inputs

Costs are calculated by multiplying the unit cost for drugs and other resources with the respective use of each of these resources.

Resource use. Clinical practice includes resource use for:

1. Surgery, VNS or ASM – including a titration phase and maintenance phase;
2. Routine disease monitoring: general practitioner (GP) visits, neurologist visits, electroencephalograms (EEG), blood sample analyses, magnetic resonance imaging (MRIs), and computed tomography's (CTs) – diversified per treatment response type and determined via expert elicitation[3];
3. The treatment of acute events: emergency department (ED) visits, GP visits, other specialist visits, and hospitalization – diversified per seizure type diversified per treatment response type and determined via expert elicitation[3]; and
4. The management of AEs, determined via expert elicitation[3] or literature[27].

Table 4. Yearly costs per patient for each treatment option (€).

	Drug costs		Adverse events				
Treatment option	Initiation year	Maint. year	Initiation year	Maint. year	Admin costs (first year)	Disease monitoring	Treatment of seizures
Cenobamate	€1,917	€1,799	€179	€107	€185	€713	€8,599
Perampanel	€1,709	€1,697	€155	€107	–	€867	€12,332
Brivaracetam	€1,303	€1,303	€107	€107	–	€844	€11,858
Lacosamide	€710	€677	€125	€107	–	€838	€11,512

Note: Initiation year includes both titration phase and maintenance phase for the remainder of the year.

Although ASMs are oral treatments, the initiation of a new ASM typically requires additional visits to the neurologist during the titration phase. This accounts for the initiation of all ASMs and was therefore assumed equal among the different treatment options. However, additional follow-up may be required in the case of the introduction of a new product the prescriber is less familiar with. To account for this, the model conservatively includes three extra consultations as an administration cost for cenobamate, while none for the other ASMs.

An overview of resource use inputs for routine monitoring, acute events management, and AE management can be found in the Supplementary Materials.

Unit costs for drugs, and other resource use (routine disease monitoring, treatment of acute events, and management of AEs), were sourced from the official NIHDI database (October 2024). Hospitalization costs related to seizure treatment were obtained from the national database on hospital resource use and costs[28] and Belgian Health Technology Assessment (HTA) guidelines[6]. Costs associated with managing AEs were collected from literature[27] and supplemented with expert opinion[3]. Table 4 provides a comprehensive overview of the annual costs for the different cost elements associated with each drug-treatment option per patient.

Results

Drug costs

Taking into account drug acquisition costs only, the introduction of cenobamate as treatment for DRE patients with FOS results in an incremental cost for the Belgian NIHDI of €462,703 in year 1 of the model, rising to €1,407,615 in year 3. This increase in the drug budget can be explained by, on the one hand, cenobamate taking market shares from cheaper treatment options such as generic lacosamide, VNS or DBS, and, on the other hand, the conservative dosing for cenobamate compared to the comparators. After 3 years, cenobamate represents a cumulative cost of €6,575,962 for the drug budget of NIHDI; however, due to replacement of other third-generation ASMs over this period, this yields a total incremental drug budget of only €2,973,075 (Figure 3).

Non-pharmaceutical costs

Non-pharmaceutical costs include drug administration costs, routine monitoring costs, acute event costs, and treatment-related AE costs. The introduction of cenobamate results in an incremental drug administration cost from €94,985 in year 1 to €86,488 in year 3 (€323,104 over the 3Y model horizon). This estimate is the result of the increased market shares of cenobamate over the model horizon in combination with the three additional neurology consultations included in the model for patients initiating cenobamate (conservative assumption), which are maintained over the model horizon.

The introduction of cenobamate results in savings for routine monitoring costs, which increase from €66,727 to €224,831 over the model horizon, resulting in a 3-year saving of €459,276, while the incremental savings for acute event management increase from €1,608,070 to €5,418,280. This is consequential to the fact that the higher efficacy of cenobamate results in a significantly improved response rate and greater seizure reduction (Figure 4), leading to lower annual cost for seizure-related treatments including outpatient visits, ER visits and hospitalizations, generating a total saving of €11,068,232 (Table 4). At last, the introduction of cenobamate only limitedly impacts costs related to the management of treatment-related adverse events: in year 1, an incremental cost for the NIHDI of 37,064 is calculated, which increases to €32,317 in year 3 of the model, resulting in a small total cost increase due to AE management (€125,713). As a consequence to the impact on non-pharmaceutical costs, the rise in the NIHDI drug budget related to the introduction of cenobamate (€2,973,075) is entirely compensated by savings at medical cost level (Figure 3). Cenobamate's efficacy, with its significantly higher response rate and seizure reduction, generates a 3-year saving of €11,078,691 for the medical cost

All cost levels

	Y1	Y2	Y3	Total
	Budget impact			
Cenobamate drug cost	€ 986.155,21	€ 2.418.454,80	€ 3.171.352,34	€ 6.575.962
Total drug budget	€ 462.702,66	€ 1.102.756,80	€ 1.407.615,32	€ 2.973.075
Medical costs	-€ 1.542.747,54	-€ 4.008.638,63	-€ 5.527.305,09	-€ 11.078.691
Total healthcare budget	-€ 1.080.044,88	-€ 2.905.881,83	-€ 4.119.689,77	-€ 8.105.616

Medical costs

Administration costs	€ 94.985,39	€ 144.630,64	€ 83.488,28	€ 323.104
Acute event (seizure) costs	-€ 1.608.069,81	-€ 4.041.883,47	-€ 5.418.279,52	-€ 11.068.233
Routine monitoring costs	-€ 66.726,80	-€ 167.717,82	-€ 224.831,32	-€ 459.276
Adverse Events costs	€ 37.063,68	€ 56.332,02	€ 32.317,48	€ 125.713
Medical costs	**-€ 1.542.747,54**	**-€ 4.008.638,63**	**-€ 5.527.305,09**	**-€ 11.078.691**

Figure 3. The total budget impact on all cost levels and medical costs alone for the NIHDI over a 3-year period (€).

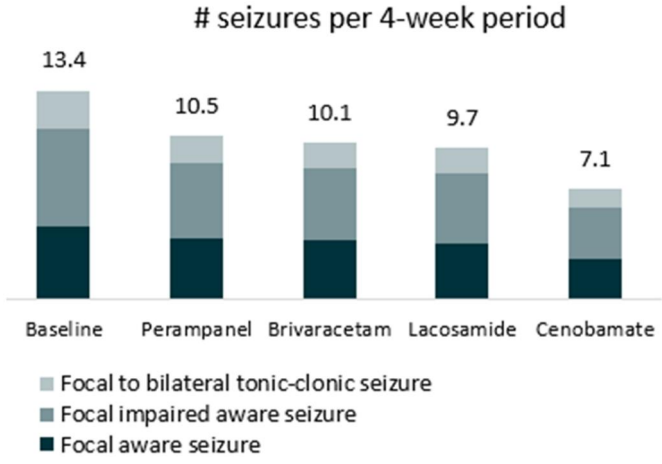

Figure 4. Number of seizures per 4-week period.

budget of NIDHI (administration, acute event, routine monitoring, and adverse event costs).

Total budget impact

Consequential to the previous, the total budget impact results in a budget saving for the NIHDI of €1,080,045 in year 1 to €4,119,690 in year 3 of the model. Therefore, the total healthcare budget for the NIHDI (combining drug and medical costs) decreases by €8,105,616 over a 3-year period following the introduction of cenobamate as a novel therapy for the adjuvant treatment of adult DRE patients with FOS, inadequately controlled despite treatment with at least three ASMs (Figure 3).

One-way sensitivity analysis

According to the OWSA, all variations from the base case consistently result in a negative budget impact (i.e. cost savings). The parameter with the biggest impact on the overall healthcare budget (−€4,120,074 in year 3) is the clinical response of cenobamate (OR; vs placebo[17]) with a budget impact range of −€1,139,669 to −€6,272,495. The parameter with the second largest impact on model outcomes is the clinical response of other ASMs (ORs; comparators vs placebo[17]) resulting in total healthcare savings between €6,128,509 and €2,446,589. The cost per acute event treatment is the third most impactful parameter, resulting in savings between €2,494,590 and €5,745,558. Parameters affecting the eligible population size (such as general population size, epilepsy prevalence, percentage FOS, and percentage of non-responders to first, second, and third ASM therapies) have a similar impact, with results ranging from €2,884,052 to €5,356,096. Varying cenobamate market shares similarly impact the total healthcare budget. The complete OWSA plot is provided as Supplementary material.

Discussion

This study aimed to assess the budget impact for the Belgian health insurer (NIHDI) if cenobamate were reimbursed for the adjunctive treatment of FOS in adult DRE patients whose disease has not been adequately controlled despite a history of treatment with at least three ASMs. The cost-effectiveness of cenobamate for this indication has already been demonstrated from a payer's perspective in the United Kingdom (UK) by Laskier et al.[15], with similar findings confirmed in Spain by Calleja et al.[29] and in Italy[20]. While similar results are anticipated for Belgium, the added value of this budget impact analysis lies in the focus on affordability rather than cost-effectiveness, which assesses whether a product provides sufficient value for money. This study comprehensively includes all cost levels for the healthcare payer (i.e. acute event costs in addition to drug, monitoring, and AE costs) when introducing a new product, and consequently provides a complete view on the impact cenobamate has on the NIHDI healthcare budget.

After 3 years, the reimbursement of cenobamate for the population under study would result in a total budget saving of €8,105,616. The results of the OWSA, allowing all parameters to vary individually 30% above and below their point estimate, appreciate this result by consistently showing cost savings after 3 years. This is in line with the results from Li et al.[5], who demonstrated net savings from a Dutch societal perspective, hence including the impact of increased productivity. However, in this study – as in ours – there is already a net saving without taking into account productivity gains. Additionally, our findings align with a budget impact analysis conducted in the United States (US), where drug costs were offset by reductions in seizure treatment costs (primarily inpatient hospitalization costs) within 1 year[30].

The generated savings for the NIHDI are driven by cenobamate's high seizure freedom rates, enhanced seizure control and high patient retention, leading to a significant reduction in costs related to acute event treatment, as the incremental impact on the drug budget itself is estimated at €2,973,075. This incremental cost is completely offset by savings for all other medical costs included in this model. The OWSA highlights that the primary driver of costs savings is cenobamate's superior profile in terms of response rate and seizure reduction compared to other ASMs. Due to the lack of head-to-head trials for third-generation ASMs, a 2022 NMA published by NICE[17] was used to model clinical efficacy. This NMA aligns with other independent NMAs and indirect treatment comparisons (ITCs) that evaluated third-generation ASMs for adjunctive treatment of FOS in adults[31–33]. Both Privitera et al.[31] and Lattanzi et al.[32] report similar ORs of cenobamate vs. placebo and comparator ASMs (brivaracetam/lacosamide/perampanel) vs. placebo, as used in the model, for $\geq$ 50% response rate and seizure freedom. Moreover, they both report statistically significant higher responses ($\geq$ 50% seizure reduction) for cenobamate versus comparator ASMs, separately[32] or collectively[31]. While no statistically significant trend favoring cenobamate over comparator treatments was identified, Lattanzi et al.[32] indicated that cenobamate had the greatest likelihood of being the best option for the $\geq$50% and 100% seizure frequency reduction. Li et al.[5] and Laskier et al.[15] make use of an alternative (not published) NMA for the comparison of treatment responses vs. cenobamate, resulting in an even more favourable profile for cenobamate. Paoletti et al.[20] makes us of a NMA published by Mulhorn et al.[33], who concluded that cenobamate was associated with increased efficacy compared with all ASMs analysed. Although there was no statistically significant differences in the outcomes, the results confirm the conclusions drawn from previous published NMAs, highlighting the important efficacy of cenobamate in comparison with other ASM. Prior to these analyses, which included cenobamate, there were few notable differences in efficacy and safety between ASMs (excluding cenobamate)[34]. Finally, NICE's technology appraisal guidance on cenobamate[35] supported the results of these ITCs[31–33] and concluded that cenobamate is cost-effective for treating drug-resistant epilepsy despite uncertainty in the clinical data and comparisons with other treatments.

While our model is based on RCT, the cenobamate profile presented is consistent with, or even conservative, compared to real-world evidence gathered through expanded access programs (EAPs) and named patient programmes (NPPs) across Europe. For example, our model estimates seizure freedom in 11.1% of patients, while Pietrafusa et al.[36] and Lasek-Bal et al.[37] report higher rates of 20.2% and 63.1%, respectively. These results were confirmed by Lauxmann et al.[38], who assessed the long-term response rates of FOS patients who switched to cenobamate after trials of at least two ASMs. After 6 months, seizure freedom was achieved by 18.4%, and significant response ($\geq$ 50% seizure reduction) by 37.9%, remaining at 30.8% at 18 months. Strzelczyk et al.[39] even report seizure freedom rates of 11.9% after 12 months, and 47.7% of patients experienced $\geq$ 50% seizure reduction.

Additionally, the proportion of non-responders in our model (34.3%) exceeds that reported in other studies, where rates were lower[39,40].

While cenobamate has a strong efficacy profile, physicians may be hesitant to change their clinical practice and adopt new treatments with which they have limited experience[41]. To account for this, varying market shares were explored in the OWSA, which showed a similar impact on the budget as epidemiological data. This confirms the robustness of the results and highlights the potential savings associated with incorporating cenobamate into Belgian clinical practice.

Strengths and limitations

Despite the positive outcomes, the strength of this study lies not only in its results but also in its comprehensive perspective, incorporating a broad range of costs, the conservative approach, making these results particularly encouraging for healthcare payers, and the use of an expert elicitation process, allowing the scientific evidence from the literature being supported by country-specific expertise, e.g. clinical practice and current and future treatment algorithms.

First, DDDs (not average study doses) were used for comparator treatments, while, for cenobamate, the average study dose calculated from the 200 mg and 400 mg treatment arms of the CO21 study was used. This resulted in an average maintenance dose of 215.1 mg per day, while the DDD for cenobamate is only 200 mg. This contrasts with Strzelczyk et al.[39], who calculated an average daily study dose of only 171.5 mg, and as such reinforces our conservative approach.

Second, the base case scenario also accounts for drug wastage. During the cenobamate titration phase 14 pills each of 50 mg, 150 mg, and 200 mg are required, while only packages of 28 pills are available. Assuming maximum wastage, the cost of three full packages was included. This conservative assumption further increases the likelihood that actual savings are larger than those calculated in the model. Third, the results are in favour of introducing cenobamate to the market, despite other ASMs being cheaper: lacosamide becoming generic (and thus cheaper) and patients switching from "other therapies" (VNS and DBS, to which no costs are associated in the model) to cenobamate, both increasing drug costs.

Fourth, starting from the ORs reported by NICE[17] results in a conservative estimate of proportions of patients responding to cenobamate. Laskier et al.[15] and Li et al.[5] report a higher proportion of patients on cenobamate achieving high to complete response. On top, our estimates being conservative is also confirmed by real-world evidence[38,39].

While this conservative approach supports the robustness of our findings, there are several limitations to this study. First, the model accounts for five response categories, in line with the reported outcomes for cenobamate[18]. However, due to a lack of comparator data, no indirect comparisons could be made for higher response levels ($\geq$75% and $\geq$90%). It was conservatively assumed, and validated by clinical experts, that ORs for these higher response levels were the same as those measured for moderate responses ($\geq$50%). This method is in line with Laskier et al.[15], Li et al.[5], and Paoletti et al.[20], who made the same assumption.

Second, the model does not include a half-cycle correction meaning it assumes all patients begin treatment on day 1 of the first model year. In reality, patients would start cenobamate at different time points throughout the year. To account for this, the market uptake for cenobamate was adjusted (i.e. decreased) in year 1 to reflect this effect. Simultaneously, by building a prevalence-based model, the model accounts for retention and patients stopping treatment and/or switching to other therapies.

Third, DRE patients are typically on multiple ASMs, with third-generation ASMs being added from the fourth treatment line onwards. These therapies were considered "background therapies" and thus not explicitly modelled. This simplification was validated by Belgian epileptologists with extensive experience in the treatment of patients with drug-resistant FOS, who indicated that the use and combination of background therapies would remain similar when cenobamate is introduced as a third-generation ASM, compared to the current situation[3]. Hence, this simplification does not affect the budget impact analysis.

Conclusion

The savings at medical cost level completely offset the impact of cenobamate on the drug budget, resulting in an overall healthcare budget saving of −€8,105,616 for the NIHDI over the first 3 years. This budget impact analysis demonstrates that introducing cenobamate as an adjunctive treatment for FOS with or without secondary generalization in adult patients with epilepsy inadequately controlled despite a history of treatment with at least three ASMs, generates important savings for the Belgian health insurance

(NIHDI). These positive outcomes can mainly be attributed to cenobamate's high efficacy, reflected in both its strong response rate and its impact on seizure frequency.

Transparency

Declaration of funding

Angelini Pharma funded this study and had a role in the report's design, analysis, interpretation, and writing.

Declaration of financial/other relationships

AT, BC, and CV are employees of Hict NV, who were commissioned by Angelini Pharma to develop and populate the economic model, perform the structured expert elicitation, and draft the manuscript. LVDB is an employee of Angelini Pharma. BL, KV, SW, and OB received financial compensation for the time to participate in the structured expert elicitation and/or advisory boards related to cenobamate. None of the authors has any other potential conflict of interest to disclose. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

KV, LV, and BL developed the idea for the study and were involved in its design. BC and AT developed and populated the model, performed the structured expert elicitation, and drafted the manuscript in collaboration with CV. KV, OB, SW, and BL participated in the data collection and the initial version of the manuscript. All authors critically reviewed the manuscript. All authors have read and approved the final manuscript. Isabelle Fau, a previous employee at Angelini Pharma, contributed to development of the idea for the study and the manuscript. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Previous presentations

The work has not been published previously.

ORCID

Kristl Vonck http://orcid.org/0000-0002-2671-2650
Olivier Bodart http://orcid.org/0000-0003-1188-5484
Benjamin Legros http://orcid.org/0000-0002-9938-7457

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