**Cost-effectiveness of cenobamate (Ontozry®) for the adjunctive treatment of focal-onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least two anti-epileptic medicinal products.**

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of cenobamate (Ontozry®). Following assessment of the Applicant's submission, the NCPE recommends that cenobamate (Ontozry®) be considered for reimbursement. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the NCPE to carry out an assessment of the Applicant's (Angelini Pharma) Health Technology Assessment of cenobamate (Ontozry®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

**About the National Centre for Pharmacoeconomics**

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

**National Centre for Pharmacoeconomics** **October 2022**

**Summary**

In December 2021, Angelini Pharma submitted a dossier of clinical, safety, and economic evidence on cenobamate (Ontozry®) for the adjunctive (i.e. add-on) treatment of focal-onset seizures (FOS), with or without secondary generalisation, in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least two anti-epileptic medicinal products (prescribed either as two separate monotherapies, or in combination). Angelini Pharma are seeking reimbursement of cenobamate on the General Medical Services (GMS) scheme. Final data was submitted by the Applicant in May 2022.

Epilepsy is a disorder of the brain characterised by repeated seizures. Approximately two thirds of people with epilepsy have focal epilepsy (previously known as partial epilepsy), in which seizures originate in one hemisphere of the brain. Focal seizures have the potential to evolve into secondary generalised seizures, in which the entire brain is affected. Drug-resistant epilepsy is defined as a failure to achieve sustained seizure freedom after adequate trials of two tolerated, appropriately chosen and used anti-seizure medicines (ASMs) (as monotherapies or in combination).

Cenobamate is a novel, small molecule with a dual mechanism of action. It acts as a positive allosteric modulator of the gamma-aminobutyric acid-A ($GABA_A$) ion channels, and reduces repetitive neuronal firing by inhibition of voltage-gated sodium channels. However, the precise mechanism of action remains unknown. Cenobamate is formulated as a film-coated tablet. It is available in five strengths ranging from 12.5mg to 200mg. Cenobamate should be taken orally, as a single dose, once daily. The recommended starting dose is 12.5mg once daily, titrated gradually over 12 weeks, to the recommended maintenance dose of 200mg once daily. Based on clinical response, the dose may be increased to a maximum of 400mg once daily. The recommended titration schedule should not be exceeded because of the potential for serious adverse reactions. Given the chronic nature of epilepsy, treatment with cenobamate could potentially be life-long.

The Applicant anticipates that cenobamate will be prescribed as a second- or subsequent-line adjunctive therapy for FOS in adult patients with epilepsy who have failed treatment with two or more previous ASMs, including at least one adjunctive therapy. This place in therapy is narrower than the product licence.

The Applicant identified five third-generation ASMs to be relevant comparators to cenobamate. These are brivaracetam, eslicarbazepine acetate, lacosamide, perampanel, and zonisamide. Neurologists in Ireland have confirmed, to the Review Group, that these reflect standard of care, in Ireland, for the second-line adjunctive treatment of FOS in adult patients with epilepsy who have failed two or more previous ASMs, including at least one adjunctive therapy.

**1. Comparative effectiveness of cenobamate**

Evidence used to inform the clinical efficacy and safety of cenobamate was taken from two phase II, double-blind, placebo-controlled, randomised controlled trials: C013 and C017. Eligible patients were aged from 18 to 65 years inclusive (up to 70 years inclusive for C017) with a documented history of FOS. In both studies, patients continued treatment with their baseline ASM regimen (comprising one to three concomitant ASMs) whilst taking study drug. In C013 (n=222), patients were randomised (1:1) to cenobamate 200mg once daily or placebo. The double-blind treatment period for C013 comprised of a six-week titration phase followed by a six-week maintenance phase. In C017 (n=437), patients were randomised (1:1:1:1) to receive either cenobamate 100mg once daily, cenobamate 200mg once daily, cenobamate 400mg once daily, or placebo. The double-blind treatment period for C017 comprised of a six-week titration phase followed by a 12-week maintenance phase. The primary endpoint in C013 was the 'Percent Change from Baseline in Seizure Frequency per 28 Days' (this was a key secondary endpoint in C017). The primary endpoint in C017 was the '50% Responder Rate', defined as a ≥50% reduction in seizure frequency (this was a key secondary endpoint in C013). In both studies all patients assigned to cenobamate at all included doses, demonstrated a greater percentage reduction in seizure frequency compared to placebo. The treatment difference, versus placebo, was statistically significant for the cenobamate 200mg and 400mg arms only; it was not statistically significant for the cenobamate 100mg arm in C017. In both studies, statistically significant greater proportions of patients assigned to any of the three doses of cenobamate achieved the 50% Responder Rate compared to placebo. An additional secondary endpoint in both C013 (post-hoc analysis) and C017 (pre-specified analysis) was 'Seizure Freedom', defined as a 100% reduction in seizure frequency during the maintenance phase. In both studies, more patients assigned to cenobamate achieved Seizure Freedom compared to placebo. The

treatment differences, versus placebo, for the cenobamate 200mg arms in C013 and C017, and for the cenobamate 400mg arm in C017, were statistically significant. The treatment difference, versus placebo, for the cenobamate 100mg arm (C017) was not statistically significant.

Additional supporting clinical evidence included an open label extension of study C017 (C017 OLE), and an ongoing phase III open-label study (C021). Study C021 (n=1,347) is primarily a safety and pharmacokinetic study of cenobamate in patients with FOS.

Direct comparative evidence for cenobamate versus the five comparators was not available. The Applicant generated indirect comparative evidence for these by conducting a series of network meta-analyses (NMAs) with outcomes including 50% Responder Rate, and Seizure Freedom. The percentages of patients who achieved the 50% Responder Rate and Seizure Freedom were statistically significantly higher with cenobamate compared to each of the five comparators.

**2. Safety of cenobamate**

During the double-blind treatment periods of C013 and C017, more patients assigned to cenobamate experienced treatment-related adverse events (AEs) compared to those receiving placebo (65.4% vs 44%, respectively). Most AEs occurred during the titration phase. AEs most commonly reported by patients receiving cenobamate included somnolence (24.7% vs 10.2% receiving placebo), dizziness (23.3% vs 15.7%), fatigue (16.1% vs 7.4%), and headache 11.3% vs 9.3%). Most AEs were either mild or moderate in severity. The frequency of moderate AEs increased with cenobamate dose.

**3. Cost effectiveness of cenobamate**

Cost-effectiveness was assessed, from the perspective of the HSE, using a Markov model with lifetime horizon. The population entering the model was adult patients with epilepsy who have FOS, and who have failed treatment with two or more previous ASMs, including at least one adjunctive therapy. This is a narrower place in therapy than the product licence. The modelled intervention was cenobamate. The dose of cenobamate was informed by data from C017, and was determined by the distribution of patients on different doses of cenobamate during the 12-week maintenance phase. Comparators were brivaracetam, eslicarbazepine acetate, lacosamide, perampanel, and zonisamide. Comparator doses were

informed by data from the NMA. Treatment with cenobamate and comparators was modelled as adjunctive therapy; patients remained on a background regimen, which was assumed to be a mix of different ASMs.

The model consisted of eleven mutually exclusive health states. Treatment effectiveness was determined by reduction in seizure frequency. Five health states were structured around patient response to treatment whilst on cenobamate or a comparator. The response rate health states are linked to the relative reduction in seizures compared to baseline, aligned with the primary outcome and secondary outcomes of the C017 study:

- No Response (<50% reduction in seizure frequency)
- Moderate Response (≥50% to <75% reduction)
- High Response (≥75% to <90% reduction)
- Very High Response (≥90% to <100% reduction)
- Complete Response i.e., seizure freedom (100% reduction)

Five health states considered patients who discontinue treatment and transition to a subsequent intervention or treatment:

- Vagal Nerve Stimulation [VNS];
- Post-VNS;
- Surgery;
- Post-surgery;
- Subsequent ASM therapy.

There was also a Death state. Model cycle length was 28 days for the first five cycles and 84 days for subsequent cycles. Data from the double blind C017 and from the open-label C017 OLE were used to inform transition probabilities for cenobamate for the 28-day and 84-day model cycles, respectively. C017 provided transition probabilities for the five response health states for cenobamate. Data for the comparators was derived by applying risk ratios, generated from the NMA, to the cenobamate transition probabilities. Discontinuation was based on parametric extrapolation, and applied equally to the five health states structured around patient response to treatment. Health related quality of life (HRQoL) was informed by EQ-5D-3L data taken from NICE clinical guideline 137 (Epilepsies: diagnosis and

management; 2012). Costs and resources considered in the model included drug acquisition, background therapy costs, subsequent treatment costs, routine monitoring costs, epilepsy event management costs, and AE costs.

Overall, the Review Group considered the model structure to be appropriate. However, there were several limitations:

1. The method by which discontinuation was applied to the response to treatment health states meant that patients in the Seizure Freedom or Very High Response health states were equally likely to discontinue treatment as those patients in the No Response health state. The Review Group considered this to be highly uncertain.
2. Outputs from the NMA were used to inform treatment effectiveness in the cost-effectiveness model. However, only two outcomes were generated for the NMA: 50% Responder Rate and Seizure Freedom. Therefore, the same risk ratio was used for multiple health states. The Review Group consider that it would have been more appropriate to consider the intermediate response health states as one (≥50% to <100% reduction in seizure frequency) due to the lack of granular data from comparator trials.
3. Data from C017, the C017 OLE, and C021 was used to inform treatment effectiveness in the model. The Applicant excluded data from C013 as the study had a shorter maintenance period than C017, lasting only six weeks compared to 12 weeks in C017. The Review Group considers it would have been preferable to use all available data to inform the cost-effectiveness model.

The Applicant presented both pairwise and incremental cost-effectiveness analyses of the costs and outcomes of cenobamate versus each of the comparators. Results of the Applicant's base case are presented in Table 1.

**Table 1: Deterministic results of the Applicant base case cost-effectiveness analyses**

| Intervention | Total costs (€) | Total QALYs | Inc. costs (€) | Inc. QALYs | Result of cost-effectiveness analyses* |
|---|---|---|---|---|---|
| Cenobamate | 195,148 | 16.34 | - | - | - |
| Zonisamide | 204,369 | 16.09 | 9,221 | - 0.25 | Dominated by cenobamate |
| Eslicarbazepine acetate | 210,584 | 16.07 | 15,437 | - 0.28 | Dominated by cenobamate |
| Perampanel | 218,444 | 16.02 | 23,296 | - 0.32 | Dominated by cenobamate |

| | | | | | |
|---|---|---|---|---|---|
| Lacosamide | 223,490 | 16.00 | 28,342 | - 0.34 | Dominated by cenobamate |
| Brivaracetam | 245,167 | 15.88 | 50,019 | - 0.47 | Dominated by cenobamate |

**inc.:** incremental; **QALY:** quality adjusted life year

* Cenobamate was more effective and less costly than each comparator in the pairwise analyses.

Discount rate of 4% for costs and outcomes applied.

To explore the uncertainty associated with each of the model limitations described above, the Review Group conducted a series of scenario analyses individually varying each relevant parameter. In all scenarios, cenobamate continued to dominate; it was demonstrated to be more effective and less costly than all comparators.

Probabilistic sensitivity analyses were conducted on the Applicant base case, varying model parameters simultaneously over 10,000 iterations. In most iterations, cenobamate is less costly and more effective than the comparators. The probability of cenobamate being cost-effective at the €45,000 threshold is 99%.

### 4. Budget impact of cenobamate

Cenobamate is available in different strengths, and marketed as titration or maintenance packs. Prices to wholesaler range from €97.52 for a 14-tablet pack of the 50mg strength up to €207.48 for a 28-tablet pack of either the 150mg or 200mg strength. The total cost per patient to the HSE (incorporating mark-up, 7.75% Framework Agreement rebate, and dispensing fees) for the 12-week titration period is approximately €609. The annual per-patient treatment cost of maintenance therapy with cenobamate is approximately €2,785 for patients prescribed 200mg once daily. For patients prescribed the maximum dose of cenobamate 400mg once daily, the annual treatment cost is approximately €5,498.

For the budget impact analysis, the Applicant considered the eligible population to be patients with epilepsy who have FOS, and who have failed treatment with two or more previous ASMs, including at least one adjunctive therapy. This is a subpopulation of the product licence. Budget impact estimates based on the full licenced population would likely be higher. The Applicant estimated 365 patients would be treated with cenobamate in year one rising to 2,133 in year five. Estimates considered mortality and discontinuation. The annual per-patient treatment cost of cenobamate was assumed to be a weighted average cost informed by the proportions of patients prescribed different doses of cenobamate

during the maintenance phase of study C017. The Applicant assumed a compliance rate of 96.6%. However, the Review Group instead assumed 100% compliance.

The Applicant estimated the gross budget impact for cenobamate to be €1.3 million in year one rising to €7.8 million in year five, with a five-year cumulative total of €22.6 million. It is anticipated that cenobamate will displace brivaracetam, eslicarbazepine acetate, lacosamide, perampanel, and zonisamide. The Applicant estimated the net drug budget impact for cenobamate to be €0.7 million in year one rising to €4.3 million in year five, with a five-year cumulative net drug budget impact of €12.4 million. Using the NCPE assumption of 100% compliance, the five-year cumulative gross and net drug budget impact estimates are €23.4 million and €12.9 million, respectively.

A net healthcare budget impact also considered potential costs and cost-offsets. Applicant and NCPE-adjusted estimates of the five-year cumulative net healthcare budget impact are €1.5 million and €2.0 million, respectively.

## 5. Patient Organisation Submissions

A patient organisation submission, from Epilepsy Ireland, was received during the course of this assessment and this will be provided to the HSE.

## 6. Conclusion

The NCPE recommends that cenobamate (Ontozry®) be considered for reimbursement as a second- or subsequent-line adjunctive therapy for FOS in adult patients with epilepsy who have failed two or more previous ASMs, including at least one adjunctive therapy *.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.