The cost-effectiveness of bempedoic acid (Nilemdo®) and bempedoic acid plus ezetimibe (Nustendi®) for the treatment of adults with primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of bempedoic acid and bempedoic acid plus ezetimibe for the treatment of adults with hypercholesterolaemia. The NCPE recommends that bempedoic acid and bempedoic acid plus ezetimibe should not be considered for reimbursement unless cost-effectiveness can be improved. 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 evaluation of the Applicant's (Daiichi Sankyo Ireland Ltd) Health Technology Assessment dossier of bempedoic acid. 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 **November 2021**

Summary

On the 30 April 2021 Daiichi Sankyo Ireland Ltd submitted a Health Technology Assessment dossier of bempedoic acid (Nilemdo®) and bempedoic acid plus ezetimibe (Nustendi®) for the treatment of adults with primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet. Reimbursement is being sought for a subgroup of the licensed indication, that is, adults with primary hypercholesterolaemia or mixed dyslipidaemia who have a high or very high cardiovascular risk when (a) the maximally tolerated statin dose in combination with ezetimibe or (b) where statins are contraindicated or not tolerated and ezetimibe monotherapy does not appropriately control low density lipoprotein cholesterol (LDL-C) levels.

Plasma LDL-C is a measure of the cholesterol mass carried by LDL particles and evidence has confirmed that the key initiating event in atherogenesis is the retention of LDL-C and other cholesterol-rich apolipoprotein (Apo) B-containing lipoproteins within the arterial wall. Cardiovascular atherosclerosis can be broadly characterised into three main entities including coronary artery disease, ischaemic cerebrovascular disease (stroke) (IS) and peripheral arterial disease (PAD). Epidemiological studies and randomised clinical trials have consistently demonstrated a log-linear relationship between the absolute changes in plasma LDL-C and the risk of atherosclerotic cardiovascular disease.

Should treatment be deemed necessary then statins are first-line therapy. If the LDL-C treatment goal is not reached with high potency statin therapy (atorvastatin, rosuvastatin) ezetimibe is added. The introduction of PCSK9 treatment (alirocumab, evolocumab) is subject to managed access and is reimbursed for patients with definite heterozygous familial hyperlipidaemia (HeFH) and those patients with a history of myocardial infarction or coronary artery bypass grafting who have an LDL-C at or above 4 mmol/l despite optimal drug therapy.

Bempedoic acid (8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid) is a small molecule that has been shown to lower LDL-C by inhibiting ATP-citrate lyase, a key enzyme in the cholesterol biosynthesis pathway that acts upstream of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the target for statins.

Bempedoic acid 180mg (Nilemdo®) is administered orally once daily. It is also available as a fixed dose combination of bempedoic acid 180mg plus ezetimibe 10mg (Nustendi®) again administered orally once a day.

1. Comparative effectiveness

The submitted dossier outlines five phase III studies in the bempedoic acid clinical programme (CLEAR) supporting product registration. CLEAR Harmony was the largest phase III trial involving 2,230 patients with atherosclerotic cardiovascular disease (97.4%), HEFH (3.8%) or both. Patients were randomly assigned in a 2:1 ratio to receive either bempedoic acid at a dose of 180mg once daily or matching placebo. The primary end-point was safety and the principal secondary endpoint was the percentage change in LDL-C at week 12 of 52 weeks. The mean baseline LDL-C was 103.2mg/dl (2.66mmol/l). At week 12 bempedoic acid reduced the mean LDL-C by 19.2mg/dl (0.5 mmol/l), representing a change of -16.5% from baseline (difference versus placebo in change from baseline was -18.1%; 95% CI, -20.0 to -16.1;$p < 0.001$). In the CLEAR Wisdom study 779 patients with atherosclerotic cardiovascular disease (94.8%), HEFH (5.2%) or both were randomised 2:1 to bempedoic acid 180mg daily or matching placebo for 52 weeks. Patients had to have an LDL-C ≥ than 70 mg/dl (1.8mmol/l) while receiving maximally tolerated lipid-lowering therapy. The mean baseline LDL-C was 120.4 mg/dl (3.1 mmol/l) and bempedoic acid lowered LDL-C significantly more than placebo at week 12 (-15% versus 2.4% respectively; difference, -17.4% (CI, -21% to -13.9%): $p<0.001$).

CLEAR Serenity included 345 patients with hyperlipidaemia and a history of intolerance to at least two statins who were randomised 2:1 to bempedoic acid 180mg or placebo once daily for 24 weeks. The primary end-point was mean percentage change from baseline to week 12 in LDL-C. The mean baseline LDL-C was 157.6 mg/dl (4.1 mmol/l). Bempedoic acid significantly reduced LDL-C versus placebo, corrected difference -21.4% (95% CI, -25.1% to -17.7%; $p<0.001$). In CLEAR Tranquility 269 patients with a history of statin intolerance and an LDL-C > 100 mg/dl (2.59 mmol/l) were treated with bempedoic acid 180mg or placebo once daily when added to ezetimibe 10mg daily for 12 weeks. The baseline LDL-C was 3.29 mmol/l and the primary endpoint was the percent change in LDL-C from baseline to week

12. Bempedoic acid added to background lipid-lowering therapy that included ezetimibe reduced LDL-C by 28.5% as compared with placebo (p<0.001).
Study 1002FDC-053 was a phase III, double-blind trial which evaluated the LDL-C lowering efficacy and safety of a bempedoic acid 180mg plus ezetimibe 10mg fixed dose combination. The 301 participants were randomised (2:2:2:1) to the fixed dose combination, placebo, ezetimibe 10mg alone and bempedoic acid 180mg alone in this 12 week study. At week 12 the fixed dose combination of bempedoic acid 180mg + ezetimibe 10mg once daily reduced LDL-C significantly more than placebo (-38%, p<0.001), ezetimibe alone (-23.2%, p<0.001) or bempedoic acid alone (-17.2%, p<0.001). Two phase II studies were described in the submitted HTA dossier as they included data for bempedoic acid 180mg and LDL-C reduction at 12 weeks and the two studies were included in the network meta-analysis.

The CLEAR Harmony–open-label extension (OLE) study assessed the long-term safety and efficacy of bempedoic acid in patients at high cardiovascular risk. After completing the 52 week CLEAR Harmony study 1462 patients entered the OLE study and received bempedoic acid for 78 weeks, followed by a 4 week washout period. The cumulative exposure to bempedoic acid was 2.5 years. At week 12 and 78 of OLE the mean LDL-C lowering from the CLEAR Harmony baseline was -14.9% and -14.4% respectively indicating a durable lipid lowering effect.

The NCPE Review Group noted the limitations of the clinical evidence including:

- short duration of many studies
- relatively small patient numbers in some of the patient subgroups
- the absence of any direct evidence of the impact of bempedoic acid on cardiovascular outcomes in patients (which will be addressed in the Clear Outcomes Study)

2. Safety

In the CLEAR Harmony study (the largest of the phase III trials; n=2230) there was no significant difference between the treatment arms with respect to either any adverse events or serious adverse events after 52 weeks when bempedoic acid was added to maximally

tolerated statin therapy. However, adverse events leading to treatment discontinuation were higher in the bempedoic acid treatment arm at 10.9% versus 7.1% in the placebo arm (p=0.005). A lower rate of new-onset or worsening diabetes mellitus was observed in the bempedoic acid arm (3.3% versus 5.4%; p=0.02), although there was a higher rate of gout (1.2% versus 0.3%; p=0.03). Whilst there was no significant difference in mortality the number of deaths in the bempedoic acid arm was 13 (0.9%) as compared with 2 (0.3%) deaths in the placebo arm. In the CLEAR Wisdom study the incidence of treatment-emergent adverse events was similar between the bempedoic acid group and the placebo group although treatment discontinuation was higher in the bempedoic acid arm (10.9% versus 8.6%). There were 6 (1.1%) fatalities in the bempedoic acid treatment group as opposed to two (0.8%) in the placebo group. In CLEAR Serenity there appeared to be higher rates of overall adverse events (64.1% versus 56.8%), serious adverse events (6.0% versus 3.6%) and adverse events leading to treatment discontinuation (18.4% versus 11.7%) in the bempedoic acid group. It is also notable that there were 9 (3.8%) adjudicated major adverse cardiac events in the bempedoic acid treatment arm compared with none in the placebo arm. Treatment-emergent adverse events, muscle-related adverse events and discontinuations were similar in the bempedoic acid and placebo groups for the CLEAR Tranquility trial. The CLEAR Outcomes study should provide more clarity in relation to the safety of bempedoic acid.

3. Cost effectiveness

The cost-effectiveness model was a Markov model developed in Microsoft Excel where the starting age was 40 years with a cycle length of one year incorporating a lifetime horizon (55 years) and the perspective was that of the Health Service Executive. The structure of the model included five ‘core’ health states including: myocardial infarction (MI), ischaemic stroke (IS), transient ischaemic attack (TIA), unstable angina (UA) and stable angina (SA). The starting point in the model depended on the patients cardiovascular history and for those who have not had a cardiovascular event i.e. primary prevention patients they started in the high risk for atherosclerotic cardiovascular disease (ASCVD) health state i.e. ‘high risk for ASCVD’ state. To allow for changing risks, costs and quality of life in the years after cardiovascular events the model includes post-event health states. These health states

include the 0 to 1 year post CV events i.e the 'core' health states (MI, IS, TIA, UA & SA), 1 to 2 year health states (non-fatal MI, non-fatal stroke, unstable angina) and 2+ years post-events (non-fatal MI, non-fatal stroke, unstable angina) by which time the risk is assumed to be stable. Patients are able to transition from any state to death (CVD or other cause death). Therefore, there were 14 health states in the model.

The baseline risks of cardiovascular events were obtained from real-world UK data including the Health Improvement Network (THIN) study and for the high-risk primary prevention patients, the QRISK3 risk algorithm was used. The relationship between the reduction of LDL-C levels and cardiovascular event risk were combined with baseline cardiovascular risk for the Irish population to estimate the health state transitions in the model. The latest Cholesterol Treatment Trialists Collaboration (CTTC) meta-analysis was used for the relationship between LDL-C and cardiovascular event risk. The source for Irish baseline characteristics, including the baseline LDL-C level of 2.9 mmol/l, came from the Irish Longitudinal Study on Ageing (TILDA) survey.

Treatment efficacy inputs are based on the reduction in LDL-C which in turn impacts on cardiovascular events. The estimates for LDL-C lowering efficacy were derived from the post-ezetimibe network meta-analysis. Health outcomes were informed by an updated systematic literature review. In the economic model health outcomes were expressed as QALYs. Utility was modelled by applying an age-adjusted baseline utility weight with multiplicative cardiovascular disutilities, which was based on Health Survey for England data. Resource usage and costs considered in the model were stratified across the following components; treatment related costs, administration and monitoring costs of drugs, health state costs and revascularisation costs.

The incremental cost-effectiveness ratio (ICER) for bempedoic acid (Nilemdo®) + ezetimibe versus ezetimibe in patients with 'statin intolerant' and patients on maximally tolerated statin therapy is shown in table 1.

Table 1. Cost-effectiveness of bempedoic acid (Nilemdo®) + ezetimibe versus ezetimibe

Population	Intervention	Total cost	Total LYG	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (Cost/QALY)
Statin	Bempedoic acid + EZE (+/- low	€32,193	11.20	7.96				

intolerant	dose statin)							
	Placebo + EZE (+/- low dose statin	€27,467	11.02	7.83	€4,726	0.19	0.13	**€35,191/QALY**
Maximally tolerated statin therapy	Bempedoic acid + statin + EZE	€33,227	11.12	7.91				
	Placebo + statin + EZE	€28,459	11.02	7.83	€4,768	0.10	0.07	**€65,338/QALY**

EZE:ezetimibe**, LYG:** life year gained, **QALY:** quality adjusted life year, **ICER:** incremental cost-effectiveness ratio
Note: A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded so calculations will not be directly replicable

The cost-effectiveness of bempedoic acid + ezetimibe (fixed dose combination; Nustendi®) versus ezetimibe in patients with 'statin intolerance' and patients on maximally tolerated statin therapy is presented in table 2.

Table 2 Cost effectiveness of bempedoic acid + ezetimibe (FDC: Nustendi) versus ezetimibe

Population	**Intervention**	**Total cost**	**Total LYG**	**Total QALYs**	**Incremental costs**	**Incremental LYs**	**Incremental QALYs**	**ICER (Cost/QALY)**
Statin intolerant	Bempedoic acid + EZE (FDC) (+/- low dose statin)	€30,841	11.20	7.96				
	Placebo + EZE (+/- low dose statin	€27,467	11.02	7.83	€3,374	0.19	0.13	€25,122/QALY
Maximally tolerated statin therapy	Bempedoic acid + EZE (FDC) + statin	€31,882	11.12	7.91				
	Placebo + statin + EZE	€28,459	11.02	7.83	€3,422	0.10	0.07	€46,900/QALY

FDC: fixed dose combination, **EZE:** ezetimibe, **LYG:** life year gained, **QALY:** quality adjusted life year, **ICER:** incremental cost-effectiveness ratio.
Note: A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded so calculations will not be directly replicable

A probabilistic sensitivity analysis (PSA) was conducted and the ICERs for bempedoic acid monotherapy (Nilemdo®) + ezetimibe versus ezetimibe were estimated at €35,500 per QALY and €67,319 per QALY in the statin intolerant and maximally tolerated statin subgroups

respectively. The probability of cost-effectiveness at the €45,000 per QALY threshold level was 74.8% and 18.8% respectively. The corresponding ICERs for the fixed dose combination (Nustendi®) were €25,574 per QALY (statin intolerant) and €47,139 per QALY (maximally tolerated statin therapy) and the probability of cost-effectiveness at the €45,000 per QALY threshold was 91% and 45.5% respectively. A deterministic sensitivity analysis indicated that the parameters impacting the cost-effectiveness to the greatest extent included the mean baseline LDL-C, the cost of bempedoic acid, the average reduction in LDL-C by bempedoic acid and the risk of cardiovascular events.

The ICERs for bempedoic acid (Nilemdo®) + ezetimibe versus the PCSK9 inhibitors exceeded €200,000 per QALY lost in the 'statin intolerant' group and exceeded €140,000 per QALY lost in the maximally tolerated statin group. Similar ICER values were obtained for the fixed dose combination therapy (Nustendi®).

4. Budget impact

Bempedoic acid drug acquisition costs applied in the model were based on a dosing schedule of 180 mg once daily. The price to wholesaler cost for bempedoic acid (Nilemdo®) and the fixed dose combination of bempedoic acid 180 mg + ezetimibe 10 mg (Nustendi®) was €47.60 per pack of 28 capsules. The total cost per patient per annum was estimated at €705.51 for bempedoic acid (Nilemdo®) or the fixed dose combination (Nustendi®).
The Applicant predicted that 1,120 patients would be treated with bempedoic acid (Nilemdo®) or the fixed dose combination (Nustendi®) in year 1 increasing to 9,052 in year 5 resulting in an estimated 5 year gross budget impact of €18.06 million. The net 5 year budget impact was estimated at €17.99 million. The NCPE Review Group considered the budget impact figures an underestimate.

5. Patient Submissions.

No patient submissions were received in support of the application.

6. Conclusion

The Review Group highlighted the limitations of the clinical evidence (short duration studies, relatively small patient numbers in some cohorts e.g. HeFH and the absence of any

direct evidence of the impact of bempedoic acid on cardiovascular outcomes) and the uncertainty in relation to the cost-effectiveness of bempedoic acid. The budget impact was also considered an underestimate.

The NCPE recommends that bempedoic acid (Nilemdo®) and bempedoic acid + ezetimibe (Nustendi®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments and that a managed access programme is introduced*.

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