

Reimbursement Recommendation

Bempedoic Acid (Nilemdo)

Indication: Primary hyperlipidemia and cardiovascular disease

Sponsor: HLS Therapeutics Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Nilemdo?

Canada's Drug Agency (CDA-AMC) recommends that Nilemdo be reimbursed by public drug plans for primary hyperlipidemia and cardiovascular disease (CVD), if certain conditions are met.

Why Did CDA-AMC Recommend Reimbursement?

The Canadian Drug Expert Committee (CDEC) determined that Nilemdo demonstrated acceptable clinical value versus ezetimibe in patients with primary hyperlipidemia and CVD. However, it was uncertain whether Nilemdo demonstrates acceptable clinical value versus alirocumab, evolocumab, or inclisiran in patients with primary hyperlipidemia and CVD. This determination was enough for CDEC to recommend that Nilemdo be reimbursed. Given that Nilemdo is expected to be an alternative lipid-lowering therapy, acceptable clinical value refers to at least comparable value versus lipid-lowering therapies other than statins.

Evidence from 1 clinical trial showed that Nilemdo, compared with placebo, reduced the risk of major cardiovascular events from happening (including death, heart attack that does not result in death, stroke that does not result in death, or surgical procedures that restore blood to parts of the heart) when given for a median follow-up of 3.4 years. This study included adults who had CVD and high levels of lipids in the blood, and who were unable to receive stable, recommended statin therapy. In those who were receiving the highest tolerated dose of statins, evidence from 2 clinical trials showed that 12 weeks of treatment with Nilemdo reduced low-density lipoprotein cholesterol (LDL-C) levels compared with placebo in the presence of CVD and high levels of lipids in the blood.

Evidence from an indirect treatment comparison showed that there was no clear difference between Nilemdo and ezetimibe for reducing LDL-C levels after 24 weeks of treatment, but that injectable lipid-lowering therapies (e.g., alirocumab, evolocumab, and inclisiran) were more effective than Nilemdo or ezetimibe at reducing LDL-C levels. The indirect treatment comparison included adults who had high levels of lipids in the blood and who had CVD or were at high risk of CVD, despite receiving stable, recommended statin therapy or being unable to receive recommended statin therapy.

Nilemdo may address an unmet need for treatment that reduces the risk of cardiovascular events in patients with high LDL-C levels who are at high risk of CVD, and who are either unable to receive stable, recommended

Summary

statin therapy, or who are already receiving the highest tolerated dose of statins.

Based on all of the preceding considerations, CDEC recommended that Nilembo be reimbursed.

Which Patients Are Eligible for Coverage?

Nilembo should only be covered for adults with a history of CVD or at high risk of CVD and who have elevated LDL-C levels.

What Are the Conditions for Reimbursement?

Nilembo should be initially covered for 3 months and may be continued if the patient shows a meaningful reduction in LDL-C of at least 10% from before treatment began with Nilembo, and the cost of Nilembo does not exceed the drug program cost of ezetimibe.

Important budget impact considerations must be addressed for health systems to be able to adopt Nilembo.

Review Background

- **Disease background:** Hyperlipidemia occurs when there are abnormally elevated levels of fat in the blood. Persistent high cholesterol damages the vascular system and results in CVD, a leading cause of death worldwide. The age-standardized prevalence of CVD in Canada was estimated to be 6,799 per 100,000 individuals in 2019. Primary hyperlipidemia is due to a genetic cause. Heterozygous familial hypercholesterolemia, a less severe form of primary hypercholesterolemia, has an estimated prevalence of 322 to 400 per 100,000 individuals.
- **Indication:** Bempedoic acid (Nilemdo) has been approved by Health Canada for:
 - Primary hyperlipidemia: “for the reduction of low-density lipoprotein cholesterol (LDL-C) in adults with hyperlipidemia, i.e., heterozygous familial hypercholesterolemia (HeFH) and mixed dyslipidemias, as an adjunct to diet, in combination with statins, with or without ezetimibe and PCSK9 inhibitors, or as an adjunct to diet, as monotherapy in patients who cannot tolerate recommended statin therapy, with or without ezetimibe and PCSK9 inhibitors.”
 - Prevention of cardiovascular events: “to reduce the risk of adverse cardiovascular events, defined as cardiovascular death, myocardial infarction, stroke, or coronary revascularisation, in adults at increased risk for these events. Nilemdo should be used with statin drug therapy, as tolerated, with or without ezetimibe and PCSK9 inhibitors. In patients unable to take statins at any dose, Nilemdo may be used as monotherapy, or combined with ezetimibe and/or PCSK9 inhibitors, as appropriate.”
- **Reimbursement request:** The sponsor is seeking reimbursement for adult patients with hypercholesterolemia who have a history of atherosclerotic cardiovascular disease (ASCVD) or who are at elevated cardiovascular risk, despite receiving stable, recommended statin therapy or being unable to receive recommended statin therapy (including those receiving no statin therapy). Bempedoic acid can be taken as monotherapy, with any dosage of statin therapy, and/or with ezetimibe.
- **Drug under review:** Bempedoic acid is a lipid metabolism regulator. It is available as a 180 mg tablet and the dosage recommended in the product monograph is 180 mg taken orally once daily.
- **Treatment costs:** At the submitted price of \$4.35 per 180 mg tablet, the annual cost of bempedoic acid is expected to be \$1,589 per patient, based on the Health Canada–recommended dosage.

Highlights of Input From Interested Parties

The patient group (HeartLife Foundation) noted the following regarding impacts of the disease, unmet needs, and important outcomes:

- Living with high cholesterol and increased cardiovascular risk is a silent disorder with no noticeable physical symptoms until a major cardiovascular event occurs, which causes persistent fear and anxiety.

- There is a need for effective and tolerable treatments that can be used long-term and do not compromise quality of life, daily functioning, and emotional well-being. The most important aspects to control are reducing the risk of cardiovascular events and reducing LDL-C levels.

The clinician groups (Riverside Cardiology and Diagnostic Imaging; Total Cardiology Rehabilitation; key opinion leaders in the management of cardiovascular risk factors; Collaborative CME and Research Network; Oakville Cardiologists; Saskatchewan Cardiologists; and St. Michael's Hospital, Unity Health Toronto, and University of Toronto) and the clinical experts consulted by CDA-AMC noted the following regarding unmet needs arising from the disease and place in therapy for the drug under review:

- Adequate LDL-C level reduction may not be consistently achievable despite lifestyle modifications, maximally tolerated statins, and ezetimibe. Access to injectable, lipid-lowering therapies (LLTs) is constrained by high cost, strict reimbursement criteria, limited coverage windows, geographic and jurisdictional variability, and patient reluctance toward injectable treatments.
- Bempedoic acid could be used in patients who are intolerant to or reluctant to try statin therapy, those who cannot access PCSK9 inhibitors or who prefer to avoid injectable therapies, and those for whom the drug represents the only effective oral treatment. In addition, it is expected to be used as an add-on therapy with or without ezetimibe for patients receiving maximally tolerated statins who require further LDL-C level reduction, offering an oral alternative before escalation to injectable therapy.

The participating public drug programs raised potential implementation issues related to considerations for initiation, discontinuation, and prescribing of therapy; care provision issues; and system and economic issues.

Recommendation

With a vote of 13 in favour to 0 against, CDEC recommends that bempedoic acid be reimbursed for primary hyperlipidemia and CVD, only if the conditions listed in [Table 1](#) are met.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adult patients with a history of ASCVD or at high risk of CVD 2. Who have elevated LDL-C levels, defined as either of the following: 2.1. LDL-C $\geq$ 2.6 mmol/L in patients who have had an adequate trial with at least 2 statins and are unable to receive stable, recommended statin therapy due to intolerance	The 2021 Canadian Cardiovascular Society dyslipidemia guidelines recommend a stepwise, LDL-C level target-driven approach starting with lifestyle modification and maximally tolerated statin therapy. Evidence from the CLEAR Outcomes study demonstrated that treatment with bempedoic acid resulted in added clinical benefit in terms of cardiovascular outcomes and LDL-C reduction for adults who had a baseline LDL-C level of at least	History of CVD: In the CLEAR Outcomes study, a documented history of CVD was defined as coronary artery disease, symptomatic peripheral artery disease, and cerebrovascular disease. High risk of CVD: Based on clinical expert input, CDEC considered that high risk of CVD may be defined as per the 2021 Canadian Cardiovascular Society dyslipidemia guidelines, which is consistent with what is being used in clinical practice in Canada. Currently,

Reimbursement condition	Reason	Implementation guidance
2.2. LDL-C $\geq$ 1.8 mmol/L in patients who are receiving a stable, optimized lipid-lowering background therapy of an effective statin dose.	2.6 mmol/L, had a history of or were at high risk for CVD, and were intolerant to statin therapy. Evidence from the CLEAR Harmony and CLEAR Wisdom studies demonstrated that treatment with bempedoic acid resulted in added clinical benefit in terms of LDL-C reduction for adults who had a baseline LDL-C level of at least 1.8 mmol/L, high cardiovascular risk, and were receiving stable, maximally tolerated statin therapy.	these guidelines state that high-risk primary prevention conditions warranting lipid-lowering therapy with a statin include most patients with diabetes, those with chronic kidney disease, and those with an LDL-C $\geq$ 5.0 mmol/L or a diagnosis of familial hypercholesterolemia. Intolerance to statin therapy: In the CLEAR Outcomes study, an intolerance to statin therapy was defined as having an adverse effect that began or worsened with statin therapy and resolved or improved upon statin discontinuation. An intolerance to statin therapy was considered when there was an intolerance to 2 or more statins at any dose, or 1 statin at any dose and the patient was unwilling or advised not to try a second statin. Based on clinical expert input, CDEC noted that the definition for an intolerance to statin therapy used in the CLEAR Outcomes study was acceptable and similar to that used in practice. CDEC noted that it would be acceptable that an intolerance to statin therapy for bempedoic acid be defined as per the reimbursement criteria of each public drug plan for drugs used for the treatment of hyperlipidemia and CVD in patients with an intolerance to statin therapy. LDL-C threshold for initiation of bempedoic acid: The LDL-C $\geq$ 2.6 mmol/L threshold in patients with an intolerance to statin therapy is based on evidence from the CLEAR Outcomes study. However, CDEC acknowledged clinician input that the CLEAR Outcomes study design does not align with clinical practice in Canada. As such, public drug plans may consider using an LDL-C threshold of 1.8 mmol/L (i.e., the same as in patients who are receiving a stable, optimized statin dose) as per the 2021 Canadian Cardiovascular Society dyslipidemia guidelines. Based on these guidelines, where the LDL-C threshold used is $\geq$ 1.8 mmol/L, public drug plans may also determine treatment eligibility using non-HDL-C $\geq$ 2.4 mmol/L, or ApoB $\geq$ 0.7 g/L.

Reimbursement condition	Reason	Implementation guidance
		Criteria alignment: Eligibility for bempedoic acid may be based on the criteria used by each of the public drug plans for reimbursement of ezetimibe for hypercholesterolemia. There is insufficient evidence that bempedoic acid is clinically superior to ezetimibe (currently reimbursed for hypercholesterolemia) and they occupy a similar place in therapy; therefore, there is no evidence that bempedoic acid should be held to a different standard than ezetimibe when considering initiation in patients with hyperlipidemia and CVD.
3. Duration of initial authorization is 12 weeks.	In the CLEAR Harmony and Wisdom studies, the change from baseline in LDL-C levels was assessed at 12 weeks.	CDEC recognized that access to appropriate prescribers may be limited in some jurisdictions, and delays in assessment may exceed typical initial authorization timelines. Therefore, public drug plans may consider extending the initial authorization period (e.g., up to 6 months) to accommodate these constraints and ensure equitable access.
Renewal		
4. For renewal after initial authorization, the physician must provide proof of clinical response to therapy, defined as a reduction of LDL-C levels of at least 10%.	CDEC considered the magnitude of the benefits observed in the trials. In the CLEAR Harmony and Wisdom studies, the differences between groups for relative LDL-C level reduction at 12 weeks were –18.1% (95% CI, –20.0% to –16.1%) and –17.4% (95% CI, –21.0% to –13.9%), respectively. In the CLEAR Outcomes study, the difference between groups for relative LDL-C level reduction at 6 months was –20.3% (95% CI, –21.1% to –19.5%). Therefore, the renewal condition is to ensure that bempedoic acid is reimbursed in patients who benefit from the treatment.	Renewal after initial authorization may be based on the criteria used by each of the public drug plans for reimbursement of ezetimibe for hypercholesterolemia. There is no evidence that bempedoic acid should be held to a different standard than ezetimibe when considering renewal in patients with hyperlipidemia and CVD.
Pricing		
5. The drug program cost of bempedoic acid should be negotiated so that it does not exceed the drug program cost of ezetimibe.	Based on the committee's assessment of the evidence, bempedoic acid is expected to have similar clinical benefits and harms compared with ezetimibe. Although bempedoic acid plus ezetimibe may lead to an increased benefit compared with ezetimibe, the committee is unable to issue a pricing condition based on the sponsor's economic evaluation due to the substantial limitations with the comparative evidence.	—

Reimbursement condition	Reason	Implementation guidance
	Therefore, the drug program cost of bempedoic acid should be no more than ezetimibe.	
Feasibility of adoption		
6. The economic feasibility of adoption of bempedoic acid must be addressed.	At the submitted price, the incremental budget impact of bempedoic acid is expected to be greater than \$40 million in years 2 and 3, and the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and the CDA-AMC estimate(s).	—

ASCVD = atherosclerotic cardiovascular disease; CDA-AMC = Canada's Drug Agency; CDEC = Canadian Drug Expert Committee; CI = confidence interval; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.

Rationale for the Recommendation

Clinical Value

Based on the totality of the clinical evidence, CDEC concluded that bempedoic acid demonstrates acceptable clinical value compared with ezetimibe in patients with primary hyperlipidemia and CVD. However, it was uncertain whether bempedoic acid demonstrates acceptable clinical value versus alirocumab, evolocumab, or inclisiran in patients with primary hyperlipidemia and CVD. Given that bempedoic acid is expected to be an alternative to LLTs other than statins, acceptable clinical value refers to at least comparable value versus LLTs other than statins.

Evidence from 1 placebo-controlled randomized controlled trial (RCT) (CLEAR Outcomes; N = 13,970) showed that treatment with bempedoic acid resulted in added clinical benefit compared with placebo for adults with primary hyperlipidemia and CVD who are intolerant to stable, recommended statin therapy. After a median follow-up of 3.4 years, bempedoic acid reduced the risk of 4-component major adverse cardiovascular event (MACE), which included cardiovascular death, nonfatal myocardial infarction (MI), nonfatal stroke, or coronary revascularization; the hazard ratio was 0.87 (95% confidence interval [CI], 0.79 to 0.96). CDEC noted that the effect of bempedoic acid was mostly driven by reductions in nonfatal MI and coronary revascularization events, while there was the possibility of no important difference in the risk of nonfatal stroke, cardiovascular death, or all-cause mortality. The treatment effect for bempedoic acid was less certain for other cardiovascular outcomes that did not include coronary revascularization, such as the risk of 3-component MACE, fatal or nonfatal MI, fatal or nonfatal stroke, and risk of cardiovascular death, due to serious imprecision.

Two placebo-controlled RCTs (CLEAR Harmony; N = 2,230 and CLEAR Wisdom; N = 779) showed that treatment with bempedoic acid resulted in a clinically meaningful reduction in LDL-C levels for adults with primary hyperlipidemia and CVD who are receiving maximally tolerated statins. After 12 weeks of treatment,

the difference between groups for relative LDL-C level reduction was 18.1% (95% CI, –20.0% to –16.1%) in the CLEAR Harmony study and –17.4% (95% CI, –21.0% to –13.9%) in the CLEAR Wisdom study. However, there is no direct evidence provided in the submission materials for the effect of bempedoic acid on cardiovascular outcomes in patients who are receiving maximally tolerated statins.

The indirect evidence from a network meta-analysis (NMA) of bempedoic acid versus other LLTs that are not statins suggested that there was no clear difference in LDL-C level reduction between bempedoic acid and ezetimibe, and that PCSK9 inhibitors were favoured over either bempedoic acid or ezetimibe monotherapy at 24 weeks. However, these results were uncertain due to imprecision and methodological limitations. Results for 52 weeks of treatment were inconclusive due to indirectness, heterogeneity, and imprecision. Because of the limited evidence, CDEC could not make conclusions on the comparative efficacy and safety of combination therapy with bempedoic acid and other LLTs that are not statins; the evidence for combination of bempedoic acid and ezetimibe included a small number of patients and pertained to LDL-C level reductions, while the combination of bempedoic acid and PCSK9 inhibitors was not properly assessed.

Bempedoic acid may address an unmet need for treatment that reduces the risk of cardiovascular events in patients with elevated LDL-C levels who are at high risk of CVD, and who are either unable to receive stable, recommended statin therapy due to intolerance, or who are receiving maximally tolerated statin therapy.

Further information on the committee's discussion around clinical value is provided in the Summary of Deliberation section.

Developing the Recommendation

The determination of acceptable clinical value was sufficient for CDEC to recommend reimbursement of bempedoic acid. As part of the deliberation on whether to recommend reimbursement, the committee also considered unmet clinical need, unmet nonclinical need, and health inequity. Information on this discussion is provided in the Unmet Clinical Need and Distinct Social and Ethical Considerations domains in the Summary of Deliberation section.

Because CDEC recommended that bempedoic acid be reimbursed, the committee also deliberated on whether reimbursement conditions should be added to address important economic considerations, health system impacts, or social and ethical considerations, or to ensure clinical value is realized. The resulting reimbursement conditions, with accompanying reasons and implementation guidance, are stated in [Table 1](#).

Summary of Deliberation

CDEC considered all domains of value of the deliberative framework before developing its recommendation: clinical value, unmet clinical need, distinct social and ethical considerations, economic considerations, and impacts on health systems. For further information on the domains of value, refer to [Expert Committee Deliberation at Canada's Drug Agency](#).

The committee considered the following key discussion points, organized by the 5 domains of value.

Clinical Value

- **Appropriate comparators:** CDEC considered ezetimibe, alirocumab, evolocumab, and inclisiran to be relevant comparators when assessing the clinical value of bempedoic acid.
- **Efficacy versus placebo:**
 - **Cardiovascular outcomes:** One double-blind, placebo-controlled RCT (CLEAR Outcomes; N = 13,970) demonstrated that treatment with bempedoic acid for a median follow-up of 3.4 years resulted in a statistically significant improvement in 4-component MACE (hazard ratio = 0.87; 95% CI, 0.79 to 0.96) compared with placebo. The results for other cardiovascular outcomes (3-component MACE and fatal or nonfatal MI) also favoured treatment with bempedoic acid over placebo, but this conclusion was less certain due to imprecision in the effect estimate. Eligible patients were adults with a history of or at high risk for CVD, with a baseline LDL-C level of at least 2.6 mmol/L, and who were intolerant to statin therapy.
 - **LDL-C level:** Two double-blind, placebo-controlled RCTs (CLEAR Harmony; N = 2,230 and CLEAR Wisdom; N = 779) demonstrated that treatment with bempedoic acid for up to 12 weeks resulted in a statistically significant improvement in LDL-C level reduction from baseline (mean between-group difference of –18.1%; 95% CI, –20.0% to –16.1% and –17.4%; 95% CI, –21.0% to –13.9%, respectively) compared with placebo. Patients eligible for either study were adults with a high risk for CVD, with a baseline LDL-C level of at least 1.8 mmol/L, and who were receiving maximally tolerated statins.
 - **Supportive evidence:** Two double-blind, placebo-controlled RCTs (CLEAR Serenity; N = 345 and CLEAR Tranquility; N = 269) enrolled patients similar to those in the CLEAR Outcomes study. However, these were smaller studies that focused on short-term change in LDL-C levels rather than cardiovascular outcomes. Therefore, the findings from these studies were included as supportive evidence for contextual interpretation. The results for LDL-C level reduction favoured treatment with bempedoic acid for up to 12 weeks over placebo. Both studies enrolled adults who had a baseline LDL-C level of at least 1.8 mmol/L and who were intolerant to statin therapy. The CLEAR Serenity study enrolled patients who required statins for primary or secondary prevention of cardiovascular events, whereas the CLEAR Tranquility study did not specify eligibility criteria related to a history of or elevated risk of CVD.
 - **Extension study:** One uncontrolled, open-label extension (OLE) study (CLEAR Harmony OLE; N = 1,462) indicated that LDL-C level reduction was maintained for up to 78 weeks of treatment. However, the results are at increased risk of bias due to the study design and imprecision. Efficacy and safety beyond 78 weeks of treatment remain uncertain, which is a limitation considering that treatment is expected to be lifelong.
 - **Combination therapy:** There was limited evidence for combination therapy of bempedoic acid and other LLTs that are not statins. Across the studies, less than 5% of patients were receiving concomitant PCSK9 inhibitors (alirocumab or evolocumab; no patients reported receiving inclisiran). In the CLEAR Outcomes, CLEAR Harmony, CLEAR Wisdom, and CLEAR Serenity studies, less than 19% of patients were receiving concomitant ezetimibe. All patients in the

CLEAR Tranquility study were receiving ezetimibe as background therapy. According to the clinical experts, the rates of concomitant therapies in these studies (except ezetimibe in the CLEAR Tranquility study) are lower than expected in current clinical practice. There were no subgroup analyses for combination therapy assessed in the trials.

- **Harms:** There were numerically more serious adverse events, adverse events leading to stopping treatment, and all-cause mortality with bempedoic acid than with placebo in the studies; CDEC noted that the difference was small and unlikely to raise clinically important concerns. Overall, CDEC concluded that the harms profile did not preclude reimbursement of bempedoic acid. Additionally, they noted that the adverse events of special interest such as gout, cholelithiasis, and tendinopathy were similar between groups (when reported), uncommon, and considered manageable. CDEC noted that the harms reported during the OLE study were generally consistent with the CLEAR Harmony study, but that long-term safety conclusions are less certain due to study design limitations.
- **Clinical importance of treatment effects:** CDEC noted that there are no known published thresholds for a clinically meaningful between-group difference for cardiovascular events. Thus, the threshold used to assess the clinical importance (i.e., 5 events per 1,000 patients) was informed by clinical expert opinion. Based on past CDA-AMC Reimbursement Reviews and confirmed by the clinical experts consulted for this review, a relative reduction of at least 20% in LDL-C levels from baseline was considered clinically meaningful. CDEC discussed how a reduction of less than 20% may still be meaningful for patients receiving statin therapy or who have lower baseline LDL-C levels. The committee also noted that, based on clinical expert suggestion, a reduction of less than 10% in LDL-C levels would likely not be clinically meaningful.
- **Certainty of the evidence:** CDEC discussed the certainty of evidence as assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method.
 - **Cardiovascular outcomes:** CDEC noted that all results for cardiovascular outcomes were in a population that is intolerant to statin therapy. The certainty was rated as high for the primary end point of time to first occurrence of 4-component MACE in the CLEAR Outcomes study and the between-group difference was clinically meaningful. The certainty was moderate for 3-component MACE and fatal or nonfatal MI outcomes and was rated down due to serious imprecision where the 95% CIs for the between-group differences crossed the threshold for a clinically meaningful difference. The certainty was low for fatal or nonfatal stroke and cardiovascular death outcomes and was rated down due to very serious imprecision where the 95% CIs for the between-group differences indicated the possibility of a benefit, harm, or a result that is not clinically meaningful.
 - **LDL-C level:** The certainty was high supporting a clinically meaningful reduction in LDL-C levels in patients who are intolerant to statin therapy (the CLEAR Outcomes study) and patients who are receiving maximally tolerated statin therapy (the CLEAR Harmony and CLEAR Wisdom studies). Although the magnitude of LDL-C level reduction was smaller in the CLEAR Harmony and CLEAR Wisdom studies versus the CLEAR Outcomes study, CDEC noted that the former studies

included patients who were receiving statin therapy and a slightly lower magnitude of reduction may be expected and was acceptable.

- **Health-related quality of life (HRQoL):** There was no evidence for the effect of bempedoic acid on HRQoL.
- **Harms:** The certainty was rated down due to imprecision and was moderate in the CLEAR Outcomes study and low in the CLEAR Harmony and CLEAR Wisdom studies.
- **Efficacy versus ezetimibe and PCSK9 inhibitors:** There was a lack of direct evidence comparing bempedoic acid versus ezetimibe or PCSK9 inhibitors in the studies. The indirect evidence from a sponsor-submitted NMA indicated no clear difference in short-term LDL-C level reduction between bempedoic acid and ezetimibe; however, PCSK9 inhibitors were favoured over either bempedoic acid monotherapy or ezetimibe monotherapy. Results for 52 weeks of treatment were inconclusive. Overall, limitations with the NMA included the lack of evidence for cardiovascular and HRQoL outcomes, substantial heterogeneity, sparse network with few closed loops, and notable imprecision in effect estimates, all of which make the results uncertain.
- **Study 053:** CDEC discussed Study 053 (N = 382), a double-blind, placebo-controlled and active comparator-controlled RCT that had similar eligibility criteria to the CLEAR Harmony and CLEAR Wisdom studies. They noted that Study 053 was smaller than the CLEAR Harmony and CLEAR Wisdom studies and it did not have direct comparisons with bempedoic acid monotherapy. Statistical comparisons were for the single pill, fixed-dose combination of bempedoic acid with ezetimibe, which is a different product and out of the scope of this recommendation. For these reasons, CDEC considered Study 053 to be supportive evidence.
- **Place in therapy:** CDEC discussed the place in therapy based on the evidence provided in the submission materials. The committee noted that bempedoic acid may be used as monotherapy, or in combination with ezetimibe. Bempedoic acid may also be used before PCSK9 inhibitors. CDEC noted that there was no evidence supporting the combination of bempedoic acid and PCSK9 inhibitors.
- **Clinical value:** Based on all of the preceding considerations, the committee determined there was comparable clinical value versus ezetimibe.



Unmet Clinical Need

- **Input on unmet clinical need:** Patients identified a need for treatment that is tolerable and reduces the risk of cardiovascular events and LDL-C levels while not compromising on HRQoL, daily functioning, and emotional well-being. CDEC acknowledged that there remains a need for additional treatment options for patients who are intolerant to statin therapy or do not achieve target LDL-C levels with available therapies. The committee discussed how the evidence for bempedoic acid supports a clinically meaningful reduction in LDL-C levels compared to placebo across all studies for patients receiving maximally tolerated statins as well as those who are intolerant to statin therapy. However, they noted that cardiovascular outcomes were only assessed in a population of patients who were intolerant to statin therapy (the CLEAR Outcomes study). CDEC agreed with the clinical

experts that, based on the established association between LDL-C level lowering and reduction in cardiovascular risk, it would be reasonable to generalize the cardiovascular outcomes results from a population that is intolerant to statin therapy to a population receiving maximally tolerated statins. Due to a lack of evidence, no conclusions could be made on the impact that bempedoic acid has on HRQoL.

- **Severity of the disease:** CDEC acknowledged that hypercholesterolemia, while often asymptomatic, can be considered both serious and chronic. The committee also recognized that CVD is a leading cause of morbidity and mortality.
- **Availability of treatment options:** CDEC discussed the stepwise approach to treatment that includes lifestyle modification and maximally tolerated statin therapy, followed by other oral (e.g., ezetimibe) or injectable (PCSK9 inhibitors) LLTs, as noted in the 2021 Canadian Cardiovascular Society dyslipidemia guidelines. The committee acknowledged that PCSK9 inhibitors are reserved for patients who are at very high risk of CVD and that access to these treatments is limited by cost and strict jurisdictional coverage criteria.
- **Significant unmet clinical need:** CDEC determined there was no significant unmet need as described in the recommendation framework in the [Procedures for Reimbursement Reviews](#) because hypercholesterolemia and CVD are not disease areas where these are challenges in evidence generation, and the available treatment options are effective for many patients.



Distinct Social and Ethical Considerations

- **Input on unmet nonclinical need:** CDEC discussed how the burdens associated with hypercholesterolemia and CVD are disproportionately higher in low socioeconomic groups as well as among First Nations, Inuit, or Métis Peoples; however, the committee noted that bempedoic acid may not be able to address this issue.
- **Equity considerations:** CDEC discussed how patients can have high LDL-C levels despite using available treatments and often can only access oral LLTs that are not statins, which have a modest effect on lowering LDL-C levels. The committee acknowledged that the cost and restrictive reimbursement criteria for PCSK9 inhibitors limit which patients can access these treatments. Moreover, CDEC noted that some patients may prefer oral drugs to injectable drugs.



Economic Considerations

- **Health impacts of bempedoic acid versus relevant comparators:** Based on the output of the economic model, bempedoic acid may be associated with a gain of 0.01 quality-adjusted life-years (QALYs) compared to ezetimibe over a lifetime (35 year) horizon, but is associated with fewer QALYs than PCSK9 inhibitors. Based on the output of the economic model, bempedoic acid plus ezetimibe may be associated with more QALYs than ezetimibe alone (0.20), and fewer QALYs than PCSK9 inhibitors.

Due to the key methodological limitations and imprecision associated with the comparative evidence for bempedoic acid with or without ezetimibe against relevant comparators, the comparative efficacy and safety are uncertain. Thus, any estimated QALY differences are highly uncertain due to the limitations with the comparative clinical evidence.

- **Cost of bempedoic acid versus relevant comparators:** Bempedoic acid is predicted to be associated with higher costs to health care systems than ezetimibe (incremental costs = \$9,674) over a lifetime (35 year) horizon, but is associated with fewer costs to health systems than PCSK9 inhibitors at the publicly available prices. Bempedoic acid plus ezetimibe is predicted to be associated with more cost to health systems than ezetimibe alone, and fewer costs to health systems than PCSK9 inhibitors.
- **Key findings of the economic evaluation and certainty of the evidence:** The economic evaluation was based on changes in LDL-C that were extrapolated to inform clinical events including MACE such as heart attacks, stroke, coronary revascularization, and death. The results were sensitive to assumptions regarding treatment discontinuation and baseline LDL-C. The clinical outcomes used in the economic model were based on an indirect treatment comparison which was associated with several limitations, including clinical and methodological heterogeneity, sparse networks and wide credible intervals, contributing to very serious imprecision and increasing uncertainty around comparative efficacy estimates. No evidence was provided to assess bempedoic acid plus a PCSK9 inhibitor.

CDEC in particular noted the uncertainty associated with the analysis of bempedoic acid plus ezetimibe and that this was informed by studies with small sample sizes. CDEC agreed that the results of the indirect evidence were uncertain, and thus the results of the economic evaluation were uncertain.

Impacts on Health Systems

- **Anticipated budget impact:** The estimated budget impact of reimbursing bempedoic acid for the treatment of the population assessed by CDA-AMC will be approximately \$137 million over the first 3 years of reimbursement compared to the amount currently spent on comparators, with an estimated expenditure of \$248 million on bempedoic acid over this period. The actual budget impact will depend on the size of the eligible patient population, market share and market uptake assumptions, the market displacement of PCSK9 inhibitors, and treatment discontinuation.

CDEC noted the incremental budget impact of reimbursing bempedoic acid is predicted to be greater than \$40 million in year 2 and year 3, and the economic feasibility of adoption must be addressed. CDEC also noted the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and the CDA-AMC estimate.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information (links to the full documents for the review can be found on the [project webpage](#)):

- the CDA-AMC review of the clinical and pharmacoeconomic evidence submitted by the sponsor, as well as relevant ethical issues related to bempedoic acid (refer to the main report and Supplemental Material document)
- the sponsor's comments on the draft report and the responses by CDA-AMC
- patients' perspectives gathered by 1 patient group, HeartLife Foundation (refer to the Patient and Clinician Group Input document)
- input from 7 clinician groups: Riverside Cardiology and Diagnostic Imaging; Total Cardiology Rehabilitation; key opinion leaders in the management of cardiovascular risk factors; Collaborative CME and Research Network; Oakville Cardiologists; Saskatchewan Cardiologists; and St. Michael's Hospital, Unity Health Toronto, and University of Toronto (refer to the Patient and Clinician Group Input document)
- input from public drug programs that participate in the reimbursement review process (refer to the Supplemental Material document)
- input from 2 clinical experts with expertise in the management of hyperlipidemia and CVD consulted by CDA-AMC.

CDEC Information

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice-Chair), Sally Bean, Daryl Bell, Dan Dunskey, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Dr. Dennis Ko, Dr. Christine Leong, Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Carla Velastegui, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: May 28, 2026

Regrets: None

Conflicts of interest: Two expert committee members did not participate due to considerations of conflict of interest.



Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

ISSN: 2563-6596

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