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## CADTH Reimbursement Recommendation

# Inclisiran (Leqvio)

**Indication:** As an adjunct to lifestyle changes, including diet, to further reduce low-density lipoprotein cholesterol (LDL-C) level in adults with heterozygous familial hypercholesterolemia (HeFH) who are on maximally tolerated dose of a statin, with or without other LDL-C-lowering therapies

**Sponsor:** Novartis Pharmaceuticals Canada Inc.

**Final recommendation:** Reimburse with conditions

# Summary

## What Is the CADTH Reimbursement Recommendation for Leqvio?

CADTH recommends that Leqvio be reimbursed by public drug plans as an adjunct to lifestyle changes, including diet, to further reduce low-density lipoprotein cholesterol (LDL-C) levels in adults who are on a maximally tolerated dose (MTD) of a statin, with or without other LDL-C–lowering therapies, and who have heterozygous familial hypercholesterolemia (HeFH), if certain conditions are met.

### Which Patients Are Eligible for Coverage?

Leqvio should only be covered to treat adult patients with HeFH according to the reimbursement criteria used for the PCSK9 monoclonal antibodies that are currently reimbursed by public drug plans.

### What Are the Conditions for Reimbursement?

Leqvio should only be reimbursed if prescribed in a similar manner as the PCSK9 monoclonal antibodies are prescribed, and if it does not cost more than the least expensive comparator reimbursed for the treatment of adult patients with HeFH who require additional lowering of LDL-C despite maximally tolerated statin therapy. Leqvio should not be reimbursed when used together with PCSK9 monoclonal antibodies.

### Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial showed that treatment with Leqvio lowered LDL-C (also known as “bad cholesterol”) in adults with HeFH who were already being treated with the highest possible dose of statins and in those who could not tolerate treatment with statins.
- Patients identified a need for treatments that are less burdensome, can reduce LDL-C as well as cardiovascular (CV) morbidity and death, are safer than existing therapies, and can improve health-related quality of life (HRQoL). While there was not enough evidence to show that Leqvio would reduce CV morbidity and death or improve HRQoL, Leqvio meets some needs identified by patients as it reduces LDL-C levels and has manageable side effects. The biannual dosing regimen may provide patients with a more manageable administration schedule.
- Based on CADTH’s assessment of the health economic evidence, Leqvio does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Leqvio compared with PCSK9 monoclonal antibodies (i.e., alirocumab and evolocumab).

# Summary

- Based on public list prices, Leqvio is estimated to cost the public drug plans approximately $440,000 over the next 3 years.

## Additional Information

### What Is HeFH?

HeFH is a genetic disease that causes high cholesterol. In Canada, it is estimated that 1 in 311 people is affected by HeFH. Individuals with HeFH have elevated LDL-C levels from a young age, and the ongoing exposure to elevated LDL-C results in a higher cumulative risk of developing atherosclerotic cardiovascular disease (ASCVD). HeFH is associated with an increased risk of CV events compared with the general population.

### Unmet Needs in HeFH

Statins are the standard treatment for lowering cholesterol, but statins alone may not help most patients with HeFH reach target cholesterol levels. Some patients with HeFH also cannot tolerate the side effects of statins. There is a need for more treatments that lower bad cholesterol and reduce CV morbidity and death in these patients.

### How Much Does Leqvio Cost?

Treatment with Leqvio is expected to cost approximately $8,518 in the first year of treatment and $5,679 in each subsequent year.

## Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that inclisiran be reimbursed as an adjunct to lifestyle changes, including diet, to further reduce low-density lipoprotein cholesterol (LDL-C) level in adults with heterozygous familial hypercholesterolemia (HeFH) who are on the maximally tolerated dose (MTD) of a statin, with or without other LDL-C–lowering therapies, only if the conditions listed in Table 1 are met.

## Rationale for the Recommendation

As outlined in the 2022 CDEC final recommendation for inclisiran, there was 1 phase III, double-blind, randomized controlled trial (RCT) (the ORION-9 trial, N = 482) that demonstrated a statistically significant improvement compared with placebo in lowering LDL-C levels in adult patients with HeFH who were receiving the MTD of a statin or who were statin intolerant. The between-group difference in percentage change in LDL-C from baseline to day 510 was −47.9% (95% confidence interval [CI], −53.5 to −42.3; $P < 0.0001$). However, clinically relevant cardiovascular (CV)–related morbidity and mortality outcomes were exploratory, and the trial was not powered to detect statistical significance for these outcomes. Additionally, it was noted that the long-term efficacy and safety of inclisiran require further review, and there is an ongoing study with a subgroup of patients with HeFH (the ORION-8 trial) that is expected to provide further evidence regarding the longer-term efficacy and safety of inclisiran in preventing pertinent clinical outcomes. As part of the evidence base for the resubmission, CDEC considered the ORION-3 and ORION-8 studies, both long-term open-label extensions, as well as a pooled analysis of safety data from 7 different ORION trials. A key methodological limitation of the ORION-3 and ORION-8 trials was the lack of a control group, and this precluded CDEC from determining whether inclisiran reduces the risk of CV morbidity and mortality; however, CDEC noted that the reductions in LDL-C were maintained throughout the longer-term follow-up. While there was insufficient evidence to evaluate the effect of inclisiran on the reduction in CV morbidity and mortality, CDEC recognized that reducing LDL-C levels is an important outcome in patients with HeFH. CDEC also noted that there did not appear to be any new safety concerns emerging from long-term use.

Patient input received for this review emphasized the need for an additional, less burdensome treatment that would lower LDL-C levels, decrease the risk of CV morbidity and mortality, have fewer side effects than existing therapies, and improve HRQoL. The ORION-9 study demonstrated that inclisiran reduces LDL-C levels compared to placebo in patients with HeFH. CDEC acknowledged that both patients and clinical experts were clear that adherence is a major issue when managing hypercholesterolemia. Each were of the opinion that inclisiran would help to address this issue and CDEC recognized that the biannual dosing regimen may provide patients with a more manageable administration schedule, although no HRQoL data were included in the trial data to specifically address this.

At the sponsor-submitted price for inclisiran and publicly listed prices for alirocumab and evolocumab, inclisiran was more costly than alirocumab and evolocumab under a 2-year time horizon. At time horizons longer than 2 years, inclisiran offered cost savings. As inclisiran is considered no more effective than alirocumab and evolocumab, the total drug cost of inclisiran should not exceed the total drug cost of the

least costly PCSK9 monoclonal antibody reimbursed for adults with HeFH who are on an MTD of a statin, with or without other LDL-C–lowering therapies.

### Table 1: Reimbursement Conditions and Reasons

| Reimbursement condition | Reason | Implementation guidance |
|---|---|---|
| **Initiation, renewal, discontinuation, and prescribing** | | |
| 1. Eligibility for reimbursement of inclisiran should be based on the criteria used by each of the public drug programs for initiation, renewal, and prescribing of the PCSK9 monoclonal antibodies (i.e., alirocumab and evolocumab) currently reimbursed to reduce LDL-C levels in adults with HeFH, with the addition of condition 2 for prescribing. | There is no evidence that inclisiran should be held to a different standard than the PCSK9 monoclonal antibodies (i.e., alirocumab and evolocumab) currently reimbursed when considering initiation, renewal, and prescribing.<br>The clinical expert noted that the place in therapy for inclisiran is comparable to that of the PCSK9 monoclonal antibodies (i.e., alirocumab and evolocumab). | — |
| 2. Inclisiran should not be reimbursed when used in combination with PCSK9 monoclonal antibodies. | There is no evidence to support the use of inclisiran in combination with PCSK9 monoclonal antibodies. | — |
| **Pricing** | | |
| 3. Inclisiran should be negotiated so that it does not exceed the drug program cost of treatment with the least costly comparator reimbursed for the treatment of adult patients with HeFH who require additional lowering of LDL-C despite maximally tolerated statin therapy. | The CADTH Clinical Review concluded there was no difference in relative efficacy between inclisiran and PCSK9 monoclonal antibodies (i.e., alirocumab and evolocumab) in adult patients with HeFH who require additional lowering of LDL-C despite maximally tolerated statin therapy. As such, there is insufficient evidence to justify a cost premium for inclisiran over the least expensive anti-PCSK9 monoclonal antibody reimbursed for adult patients with HeFH who require additional lowering of LDL-C despite maximally tolerated statin therapy. | — |

HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol.

## Discussion Points

- The sponsor requested a reconsideration of the initial CDEC draft recommendation not to reimburse inclisiran as an adjunct to lifestyle changes, including diet, to further reduce LDL-C levels in adults with HeFH who are on the MTD of a statin, with or without other LDL-C–lowering therapies. There were 3 issues outlined by the sponsor in the request for reconsideration that were discussed by CDEC. The first issue was that the sponsor was of the view that the CDEC draft recommendation not to reimburse was inconsistent with the evidence standard applied to all other reimbursed LDL-C–lowering therapies for HeFH and with clinical guidelines. Regarding the second issue, the sponsor stated that the CDEC draft recommendation did not consider the pathophysiology of HeFH.

Regarding the third issue, the sponsor was of the view that the CDEC draft recommendation did not seem to adequately consider clinician input.

- During the initial meeting, CDEC noted that the ORION-9 trial was the only pivotal ORION trial that included an HeFH population; therefore, none of the pooled analyses submitted by the sponsor were relevant for the HeFH indication. The incidence of major adverse cardiac events (MACEs) in the ORION-9 trial was similar for inclisiran (4.1% of patients) and placebo (4.2% of patients); therefore, there was no evidence that inclisiran reduced the risk of CV morbidity and mortality in the HeFH population. During the reconsideration meeting, CDEC acknowledged the input from the clinical experts consulted by CADTH and the clinician groups. The clinical experts suggested that due to the natural course of HeFH, and the fact that there has never been a trial of adequate duration and size performed with any PCSK9 monoclonal antibodies to reveal differences between PCSK9 monoclonal antibodies and placebo for clinical outcomes such as CV morbidity and mortality, it is unlikely 1 will be done with inclisiran.
- CDEC discussed the post hoc pooled analysis of MACEs from the ORION-9, ORION-10, and ORION-11 trials submitted by the sponsor. However, they noted that the analysis had some limitations and potential biases. The primary issue is that MACEs and their components were only an exploratory outcome. Sample sizes were not determined based on these outcomes, and definitions may not have been inclusive or specific enough. Events were captured via the safety population, and there was no blinding or centralized assessment of events, which introduces potential for bias. Moreover, the use of a post hoc analysis introduces significant potential for bias, as an investigator may be influenced by their ability to see the data when deciding what analyses to conduct and how to construct the composite outcome. The selection of trials for post hoc pooling also mixed the populations with HeFH and populations with nonfamilial hypercholesterolemia (nFH) with atherosclerotic cardiovascular disease (ASCVD), as was done with the ORION-9, ORION-10, and ORION-11 trials. Moreover, the post hoc analysis of MACEs in the ORION-9 trial showed no difference between inclisiran and placebo.
- During the reconsideration meeting, CDEC acknowledged the input from the clinical experts consulted by CADTH and the clinician groups who noted that HeFH is a genetic disorder characterized by lifelong elevation of LDL-C, which leads to premature onset of atherosclerosis, ultimately resulting in a higher frequency and earlier onset of adverse CV events. CDEC recognized that reducing LDL-C levels is therefore an important outcome in patients with HeFH. CDEC also recognized that there is a health need for patients who do not reach LDL-C targets despite available treatments.
- CDEC noted that the ORION-4 study — which was described in the recommendation issued in 2022 as a potential source of data for CV morbidity and mortality — featured a population with ASCVD, and while it was unlikely to be relevant for the population with HeFH, it would provide further evidence to better characterize the efficacy and safety of inclisiran in preventing pertinent clinical outcomes. These outcomes include the reduction of CV events, CV-related death, and all-cause mortality, and hence contribute valuable information regarding the long-term safety and efficacy of inclisiran.

- In the recommendation issued for inclisiran in 2022, CDEC noted that there was no evidence that inclisiran would be better tolerated in patients who did not respond to or were intolerant to PCSK9 monoclonal antibodies, and that the efficacy of switching from PCSK9 monoclonal antibodies to inclisiran for reduction in LDL-C levels and CV morbidity and mortality was unknown. CDEC noted that there was no new evidence submitted by the sponsor that would change this.
- Given that hypercholesterolemia requires lifelong treatment, CDEC noted at the time of the 2022 recommendation that there was uncertainty regarding the long-term efficacy and safety of inclisiran for the treatment of HeFH. CDEC also noted that the novel mechanism of action for inclisiran added to the uncertainty. The ORION-3 trial (4-year open-label extension of the phase II ORION-1 trial) and ORION-8 trial (3-year open-label extension of the ORION-3 trial, as well as the ORION-9, ORION-10, and ORION-11 long-term extension trials) provided some evidence that the reduction in LDL-C seen in the ORION trials was durable, and there was no evidence of new safety issues. However, any conclusions that could be drawn from these trials were limited by the lack of MACE outcomes, lack of comparator group, and lack of blinding.
- In the recommendation issued for inclisiran in 2022, CDEC discussed the lack of direct comparative evidence for inclisiran versus PCSK9 monoclonal antibodies or other add-on agents (such as ezetimibe). They noted that 1 sponsor-submitted indirect treatment comparison (ITC) suggested that inclisiran does not have a consistent or distinct difference in efficacy in LDL-C reduction compared to evolocumab or alirocumab, although they also noted uncertainty about the ITC results due to the inherent heterogeneity across trials in the networks, and that the duration of follow-up (24 weeks) was short given the chronic nature of the condition. No additional ITCs were provided for the resubmission.

## Background

In Canada, cardiovascular disease (CVD) is the second leading cause of death and accounted for almost 20% of all deaths in 2020. Despite its pathophysiological complexity, the 1 prerequisite for atherosclerotic plaque development is the presence of LDL-C. Hypercholesterolemia can be grouped into 2 forms: nFH and familial hypercholesterolemia (FH), which is also referred to as acquired or genetic hypercholesterolemia. nFH is characterized by elevated LDL-C levels. Its etiology is likely due to a complex interplay between several genetic and environmental risk factors that increase the risk of nFH, including diet, smoking, physical inactivity, and other factors known to be associated with an increased risk of CVD (e.g., diabetes, chronic kidney disease, and hypertension). In Canada, the 1-year incidence rate for ASCVD ranges from 7.2 to 8.8 per 1,000 person-years, and the 5-year prevalence of ASCVD ranges from 6.91% to 8.55% in adults.

Elevated LDL-C is directly associated with the development of atherosclerosis and ASCVD. The 3 main subcategories of ASCVD are coronary artery disease, CVD, and peripheral arterial disease (PAD). Individuals with hypercholesterolemia and a history of an atherosclerotic event are categorized as having established clinical ASCVD (i.e., they are secondary prevention patients), while individuals with hypercholesterolemia at risk of developing ASCVD are considered primary prevention patients. A subset of primary prevention

patients at greater risk of ASCVD are referred to as having ASCVD risk equivalent (ASCVD-RE). Patients with ASCVD-RE are defined as those with type 2 diabetes mellitus or FH, or with a 10-year risk of a CV event greater than or equal to 20% as assessed by the Framingham Risk Score (FRS) for CVD or equivalent. The proportion of the overall population with ASCVD who are considered to be at high risk is estimated to be approximately 25%. Following Canadian guidelines, published literature, and validation with clinicians in Canada, patients with nFH and ASCVD who are deemed to be at high risk are defined as patients with any of the following criteria: diabetes, recurrent vascular events, PAD, or acute coronary syndrome (ACS) in the past 12 months, and with LDL-C levels greater than 1.8 mmol/L despite taking MTD statins with or without other lipid-lowering therapies. Throughout this report, the high-risk ASCVD subgroup refers to patients with any of these criteria.

FH is 1 of the most common genetic disorders and is caused by mutations in the genes encoding LDLR, apo-B, or PCSK9, leading to high plasma levels of LDL-C. Depending on the number of mutant alleles, patients can be categorized as having homozygous FH (HoFH) or heterozygous FH (HeFH). HeFH has an estimated prevalence of approximately 1 in 250 individuals to 1 in 311 individuals. The clinical presentation of FH is variable, affected by the number and type of mutations together with other genetic factors. Individuals with FH have elevated LDL-C levels from a young age, and the ongoing exposure to elevated LDL-C results in a higher cumulative risk of developing ASCVD. Patients with FH may present with physical findings such as tendon xanthomata or xanthelasma. FH is associated with an increased risk of CV events compared to the general population.

Inclisiran has a Health Canada indication as an adjunct to lifestyle changes, including diet, to further reduce LDL-C levels in adults with the following conditions who are on MTD of a statin, with or without other LDL-C–lowering therapies: HeFH, or nFH with ASCVD.

Inclisiran is a double-stranded, small interfering RNA that causes the degradation of PCSK9 mRNA. It is available as a subcutaneous injection through a single-dose, prefilled syringe. The Health Canada–approved dose for this indication is 284 mg administered as a single subcutaneous injection initially and again at 3 months, then every 6 months thereafter.

## Submission History

Inclisiran was previously reviewed by CADTH in February 2022 for the same indication, and the recommendation was not to reimburse. Key reasons for this recommendation included the fact that there was insufficient evidence showing inclisiran reduced CV morbidity and mortality, or all-cause mortality, as the pivotal ORION-9, ORION-10, and ORION-11 trials were not designed to assess these outcomes. Additionally, CDEC noted that the long-term efficacy and safety of inclisiran had not been determined, and that there were 2 ongoing studies (the ORION-4 and ORION-8 studies) that are expected to provide further evidence to better characterize the pertinent clinical outcomes and provide long-term efficacy and safety data. CDEC also noted that there was no direct comparison of inclisiran to evolocumab or alirocumab, or other add-on agents, and

that there were limitations with the submitted ITC, including the relatively short follow-up (24 weeks) for a chronic condition.

The sponsor outlined the basis for their resubmission. In an effort to address the lack of evidence for reduction of CV morbidity or mortality and all-cause mortality, the sponsor included a post hoc pooled analysis of MACEs in the pivotal ORION studies. To address concerns over long-term efficacy and harms, the sponsor included the findings of the long-term ORION-3 and ORION-8 extensions. To address the issue of a lack of long-term safety data, in addition to the ORION-3 and ORION-8 studies, the sponsor submitted a pooled analysis of 7 ORION trials. Finally, the sponsor submitted a revised budget impact model to address CADTH's concerns from the first recommendation.

## Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 RCT in adult patients with HeFH
- a review of post hoc pooled analyses of MACEs in the pivotal ORION studies
- a review of 2 long-term extension studies (the ORION-3 and ORION-8 studies)
- patients' perspectives gathered by 2 patient groups (the Canadian Heart Patient Alliance [CHPA] and the HeartLife Foundation)
- input from public drug programs that participate in the CADTH review process
- input from 3 clinical specialists with expertise diagnosing and treating patients with HeFH and nFH with ASCVD
- input from 14 clinician groups, including the Alberta Cardiovascular Disease Prevention Collaborative; BC Lipid Specialists; Centre hospitalier universitaire Dr-Georges-L.-Dumont; Cambridge Cardiac Rehab Program; Canadian Cardiovascular Society (CCS) Dyslipidemia Guideline Committee; Cardiology Association of Niagara; Egyptian Cardiologists of Niagara; Kawartha Cardiology Clinic; Lipid Clinic of McMaster University and Hamilton Health Sciences; Mazankowski Alberta Heart Institute; Oakville Cardiologists; Service of Cardiology, Internal Medicine Department and Heart Failure Group at St. Thomas Elgin General Hospital; Western University, Division of Cardiology, Cardiac Rehabilitation and Secondary Prevention Program; and University of Toronto faculty and clinicians at St Michael's Hospital who were actively involved in the treatment of patients with ASCVD and/or lipid disorders
- a review of the pharmacoeconomic model and report submitted by the sponsor.

# Stakeholder Perspectives

## Patient Input

Two patient groups provided input via survey and interviews (the CHPA) and responses from executives (the HeartLife Foundation).

The patient input described a condition that is very difficult to manage, impacts patients' physical and mental well-being, has a significant financial burden on families, and impacts their quality of life. Symptoms like shortness of breath, chest pain, and fatigue were reported by the respondents, who also noted the negative impact of a heart attack, bypass surgery, or stroke on themselves and their families. Many with a family history of heart disease and/or high cholesterol commented on their fear of following a family pattern of early death.

Adherence and access to newer treatments (such as PCSK9 monoclonal antibodies) were identified by patients as key challenges in managing their condition. Patients emphasized the importance of having a safe, tolerable, and effective treatment to maintain their LDL-C levels below recommended thresholds. Patients also noted the importance of having a less frequent dosing regimen in managing their condition.

The patient groups stated that patients seek a safe, tolerable, and effective treatment that can minimize long-term health consequences by effectively managing LDL-C levels below the recommended threshold. They noted that patients also want an accessible therapy with a more affordable and manageable treatment regimen, less frequent dosing, fewer side effects, easier administration, and less disruption to work or daily life.

## Clinician Input

### Input From Clinical Experts Consulted by CADTH

Nonadherence, intolerance to high-intensity statins, inability to reach recommended lipid targets despite the MTD of statins and ezetimibe, and lack of access to PCSK9 monoclonal antibodies were the major unmet needs identified by the clinical experts in treatment of patients with HeFH, or nFH with ASCVD. Accordingly, the clinical experts believed that in addition to being another PCSK9-targeting drug, inclisiran may help with nonadherence due to the less frequent dosing schedule.

The clinical experts believed that for patients with HeFH — in addition to those patients unable to reach LDL-C targets despite taking the maximally tolerated statin with or without ezetimibe — patients who would be especially well-suited to treatment with inclisiran would include those with other risk factors, such as smoking, diabetes, hypertension, or elevated Lp(a). For patients with nFH with ASCVD, the clinical experts believed that well-suited patients would include those unable to tolerate high-intensity statins, those with early disease onset or recurrent disease, those whose LDL-C is far from the recommended threshold, and those with the risk factors identified for patients with HeFH. The clinical experts also referenced the 2021 CCS guidelines, which identified the secondary prevention patients who would be likely to derive the most benefit from intensification of statin therapy with the additional use of a PCSK9 monoclonal antibody. These included patients with recent ACS (within the previous 52 weeks), diabetes mellitus or metabolic syndrome,

polyvascular disease, symptomatic PAD, recurrent myocardial infarction (MI), MI in the previous 2 years, previous coronary artery bypass graft, LDL-C of 2.6 mmol/L or greater or HeFH, or Lp(a) of 120 nmol/L or greater.

The clinical experts noted that genetic testing should not be required to confirm diagnosis of HeFH, due to the lack of availability of testing, and they also noted that HeFH is underdiagnosed in Canada. Various lipid parameters would be used to assess response to treatment in addition to LDL-C, including non–high-density lipoprotein cholesterol (non–HDL-C) and apo-B. Although there is no recent guidance on how frequently to assess response, after the initial titration, response is typically assessed every 6 to 12 months.

### Clinician Group Input

Fourteen clinician groups provided input: the Alberta Cardiovascular Disease Prevention Collaborative (8 clinicians contributed to the input); BC Lipid Specialists (11 clinicians contributed to the input); Centre hospitalier universitaire Dr-Georges-L.-Dumont (6 clinicians contributed to the input); Cambridge Cardiac Rehab Program (6 clinicians contributed to the input); CCS Dyslipidemia Guideline Committee (14 clinicians contributed to the input); Cardiology Association of Niagara (3 clinicians contributed to the input); Egyptian Cardiologists of Niagara (3 clinicians contributed to the input); Kawartha Cardiology Clinic (7 clinicians contributed to the input); Lipid Clinic of McMaster University and Hamilton Health Sciences (1 clinician contributed to the input); Mazankowski Alberta Heart Institute (3 clinicians contributed to the input); Oakville Cardiologists (9 clinicians contributed to the input); Service of Cardiology, Internal Medicine Department and Heart Failure Group at St. Thomas Elgin General Hospital (5 clinicians contributed to the input), Western University, Division of Cardiology, Cardiac Rehabilitation and Secondary Prevention Program (3 clinicians contributed to the input); and University of Toronto faculty and clinicians at St Michael's Hospital who are actively involved in the treatment of patients with ASCVD and/or lipid disorders.

The clinician groups agreed that the major issues with managing hypercholesterolemia — whether it be in patients with HeFH or patients with nFH with ASCVD — are adherence (as well as intolerance) and lack of accessibility of drug therapies, and that the main outcome of interest is reduction in lipid parameters (LDL-C, non–HDL-C, and apo-B) at 6 months initially and then assessed annually thereafter.

The clinician groups believed that inclisiran would be best suited for patients at risk of ASCVD or with FH who require additional lipid-lowering therapy, who become refractory to statins and ezetimibe, along with those who experience adherence or tolerability issues.

## Drug Program Input

Input was obtained from the drug programs that participate in the CADTH Reimbursement Review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for inclisiran:

- relevant comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy

- considerations for discontinuation of therapy.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

## Table 2: Responses to Questions From the Drug Programs

| Implementation issues | Response |
|---|---|
| **Relevant comparators** | |
| The ORION-9, ORION-10, and ORION-11 trials were all placebo controlled. There were no head-to-head trials comparing inclisiran to other therapies. | This was a comment from the drug programs to inform CDEC deliberations. |
| The PCSK9 monoclonal antibody therapies are only reimbursed for HeFH by the public drug programs. Reimbursement for indications beyond HeFH (i.e., ASCVD) will be associated with a large budget impact due to the expected population size that would be eligible for treatment. | This was a comment from the drug programs to inform CDEC deliberations. |
| **Considerations for initiation of therapy** | |
| Is genetic testing required to make the diagnosis of HeFH or is this determined only clinically? | The clinical experts noted to CDEC that genetic testing is not required to make the diagnosis of HeFH. It is also not available across Canada, and making it a requirement would result in inequities in access. |
| How is diagnosis of HeFH confirmed? In some jurisdictions, definite or probable diagnosis of HeFH using the Simon Broome or Dutch Lipid Network criteria or genetic testing is used; should diagnosis of HeFH be confirmed in a similar manner before initiating inclisiran? | The clinical experts noted to CDEC that new criteria have emerged in the past 3 years, based on work performed by researchers in Canada, indicating that a diagnosis of FH should be considered in patients with a baseline LDL-C of 5 mmol/L or greater for patients aged at least 40 years (or LDL-C ≥ 4.0 mmol/L for those aged < 18 years, or LDL-C ≥ 4.5 mmol/L for those aged ≥ 18 years and < 40 years). The presence of 1 or more major criteria (DNA mutation, tendon xanthomas, LDL-C ≥ 8.5 mmol/L) establishes a diagnosis of definite FH. Genetic testing is not necessary for diagnosis, and approximately 30% of patients with a definitive diagnosis of HeFH do not display a monogenic variant. This is now accepted by Canadian guideline committees. |
| Inclisiran is to be used as an adjunct to the MTD of a statin.<br>• What if the patient is statin intolerant? Would inclisiran be used as monotherapy?<br>• For how long would the MTD of a statin be used before adding inclisiran?<br>• Does statin intensity matter (any statin vs. high-intensity statin)?<br>• In the trials, patients not receiving a statin must have had documented evidence of intolerance to all doses of at least 2 different statins; should such criteria be applied before initiating inclisiran?<br>• There is a discrepancy in the definition of adherence to the MTD of statins used by jurisdictions. What is considered "adherent" to MTD statins? | The clinical experts agreed that inclisiran could be used as monotherapy if a patient is intolerant to statins.<br>The clinical experts noted that the length of trial of a statin before moving to inclisiran is somewhat arbitrary; however, 3 months would be a reasonable estimate.<br>With respect to the question about whether statin intensity matters, the clinical experts noted that new data suggest that the better approach may be to use a moderate intensity statin along with ezetimibe, rather than pushing for an MTD of a statin. The clinical experts did believe that a trial of a high-intensity statin may be worthwhile; however, they also noted that if a patient is far from their target, then it is unlikely that doubling the statin dose and adding ezetimibe would be sufficient to achieve their target LDL-C.<br>The clinical experts believed that patients trialling 2 different statins would be reasonable, and this is widely accepted.<br>For MTD, the clinical experts believed that one needs to rely on patient |

| Implementation issues | Response |
|---|---|
| | testimony when it comes to intolerance, and adherence is essentially defined as whether or not the patient is taking the drug.<br>CDEC recommended that eligibility for reimbursement of inclisiran should be based on the criteria used by each of the public drug programs for initiation, renewal, and prescribing of the PCSK9 monoclonal antibodies (i.e., alirocumab and evolocumab) currently reimbursed to reduce LDL-C levels in adults with HeFH. CDEC also noted that MTD should align with what was used in the trials and that an MTD of statins, not a moderate-intensity approach, should be implemented. |
| Should ezetimibe or other nonstatin, lipid-lowering therapies be used before starting inclisiran? | Reflecting the Canadian Cardiovascular Society 2021 guidelines, if the LDL-C level is slightly above the recommended threshold (1.8 to 2.2 mmol/L), then adding ezetimibe makes sense according to the clinical experts; however, if the LDL-C level is greater than that (> 2.2 mmol/L, for example), then the ezetimibe step is not worthwhile. The clinical experts believed that other LLTs like bile acid–binding resins are not a viable option due to their tolerability issues. |
| Many jurisdictions require a trial of ezetimibe before reimbursing PCSK9 monoclonal antibodies for the treatment of HeFH. For example:<br>• confirmed adherence to high-dose statin (e.g., atorvastatin 80 mg or rosuvastatin 40 mg) in combination with ezetimibe for at least a total of 3 months<br>• confirmed adherence to ezetimibe for at least 3 months and inability to tolerate high-dose statin.<br>Should such criteria be applied before initiating treatment with inclisiran? | The clinical experts believed that these criteria should not be required before being eligible for inclisiran.<br>CDEC recommended that eligibility for reimbursement of inclisiran should be based on the criteria used by each of the public drug programs for initiation, renewal, and prescribing of PCSK9 monoclonal antibodies (i.e., alirocumab and evolocumab) currently reimbursed to reduce LDL-C levels in adults with HeFH. |
| Should the initiation criteria for inclisiran be aligned with those for alirocumab and evolocumab in patients with HeFH? | CDEC and the clinical experts agreed that the initiation criteria for inclisiran should be aligned with that of alirocumab and evolocumab in patients with HeFH. |
| **Considerations for continuation or renewal of therapy** | |
| Should the renewal criteria for inclisiran be aligned with those for alirocumab and evolocumab in patients with HeFH?<br>Note: While CADTH recommendations for alirocumab and evolocumab do not include renewal criteria, some jurisdictions do have renewal criteria. | The clinical experts noted to CDEC that the current requirement is for a 40% reduction in LDL-C after a 4-month trial; however, inclisiran is given every 6 months, so these criteria do not align.<br>The clinical experts were of the opinion that although a timeline of 12 months for renewal would make more sense than 4 months, the requirement for renewal creates unnecessary administrative burden at multiple levels. The clinical experts also noted that the 40% threshold is not based on evidence; the more important target is for the patient to be reaching their targets for LDL-C.<br>CDEC recommended that renewal criteria of inclisiran should be based on the criteria used by each of the public drug programs for renewal of PCSK9 monoclonal antibodies (i.e., alirocumab and evolocumab) currently reimbursed to reduce LDL-C levels in adults with HeFH. |

| Implementation issues | Response |
|---|---|
| **Considerations for discontinuation of therapy** | |
| If a patient using inclisiran for primary prevention experiences a heart attack or stroke, should the patient continue using inclisiran for secondary prevention? | The clinical experts noted to CDEC that these patients should continue on the drug, and likely need more aggressive intervention. |
| Should the discontinuation criteria for inclisiran be aligned with those for alirocumab and evolocumab in patients with HeFH?<br>Note: While the CADTH recommendations for alirocumab and evolocumab do not include discontinuation criteria, some jurisdictions do have discontinuation criteria. | The clinical experts stated that patients whose condition has not responded should have the drug discontinued; however, nonresponse to PCSK9 monoclonal antibodies is rare. In most cases, nonresponse is usually due to administration error.<br>Otherwise, the clinical experts agreed that discontinuation should be considered for patients who are intolerant to inclisiran, or patients who have a competing illness that makes use of inclisiran no longer necessary.<br>CDEC recommended that discontinuation criteria of inclisiran should be based on the criteria used by each of the public drug programs for discontinuation of PCSK9 monoclonal antibodies (i.e., alirocumab and evolocumab) currently reimbursed to reduce LDL-C level in adults with HeFH. |

ASCVD = atherosclerotic cardiovascular disease; CABG = coronary artery bypass graft; CDEC = Canadian Drug Expert Committee; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; LLT= lipid-lowering therapy; MI = myocardial infarction; MTD = maximally tolerated dose; PAD = peripheral artery disease.

# Clinical Evidence

## Systematic Review

### Description of Studies

The major focus of this resubmission was a post hoc pooled analysis of MACEs from the ORION-9, ORION-10, and ORION-11 trials. These trials, all included in the original submission, were phase III, double-blind RCTs comparing inclisiran to placebo in adult patients with HeFH (the ORION-9 trial) or ASCVD (the ORION-10 and ORION-11 trials) and ASCVD-RE (i.e., those with diabetes, FH, or a 10-year risk of a CV event ≥ 20% as assessed by the FRS for Cardiovascular Disease or equivalent) (the ORION-11 trial) who were receiving MTD statins, or who were statin intolerant. Patients in the ORION-9 trial had a history of HeFH with a diagnosis of HeFH by genetic testing or phenotypic Simon Broome criteria, and/or a documented history of untreated LDL-C greater than 190 mg/dL and a family history of FH, elevated cholesterol, or early heart disease. In all 3 ORION studies, patients were randomized 1:1 to either inclisiran sodium 300 mg or placebo in addition to MTD statin. The ORION-9, ORION-10, and ORION-11 trials enrolled 482 patients, 1,561 patients, and 1,617 patients, respectively. The studies were all 18 months in duration with patients receiving four 300 mg doses of inclisiran sodium on day 1, day 90, day 270, and day 450. The primary outcome of the ORION-9, ORION-10, and ORION-11 trials was the percent change in LDL-C from baseline to day 510. In all trials, the co-primary end point was the average percentage change in LDL-C from baseline over the period after day 90 and up to day 540, reflecting the start of the biannual dosing regimen. Incidences of CV death, resuscitated cardiac arrest, nonfatal MI, and nonfatal stroke (ischemic and hemorrhagic) were exploratory outcomes in

the ORION trials within the composite outcome of MACEs, and total deaths were considered a secondary outcome reported as an adverse event (AE) in the ORION studies.

Baseline characteristics of the ORION trials were balanced between groups and generally applicable to the population in Canada. The ORION-9 trial enrolled patients with a median age of 56 years and a relatively even ratio of males and females (47.1% male, 52.9% female) with either ASCVD (27.4%) or ASCVD-RE (72.6%). A total of 73.9% of patients were on high-intensity statins at baseline, with 25.3% either partially or completely intolerant to statins, and 52.3% were treated with ezetimibe. The ORION-10 trial enrolled mostly males (69.4%) with a median age of 67 years, all with ASCVD (91.1% with coronary heart disease). Approximately two-thirds (69.4%) of patients were on a high-intensity statin at baseline, with 22.0% partially or completely intolerant. A total of 9.9% of patients were treated with ezetimibe. ORION-11 enrolled patients with ASCVD (87.4%) and ASCVD-RE (12.6%). Patients were mostly male (71.7%) with a median age of 65 years. A total of 78% of patients were receiving high-intensity statins, while 11.4% were considered partially or completely intolerant, and 7.1% of patients were treated with ezetimibe.

### Efficacy Results in Patients With HeFH

#### *Major Adverse Cardiac Events*

In the ORION-9, ORION-10, and ORION-11 trials, the exploratory end point of MACEs was defined as the composite of CV death, cardiac arrest, nonfatal MI, and nonfatal stroke (hemorrhagic or nonhemorrhagic), using a predefined Medical Dictionary for Regulatory Activities (MedDRA) search.

As part of their resubmission, the sponsor conducted a pooled analysis of clinical outcomes from the ORION-9, ORION-10, and ORION-11 trials, and they also provided what they referred to as a sensitivity analysis that pooled data from the ORION-10 and ORION-11 studies. The pooled analysis of all 3 trials is not relevant for this review, as it combines the population with HeFH with the population with nFH and ASCVD, and these 2 populations are being viewed separately for this review, consistent with the indication. The sensitivity analysis that was conducted to assess the effects of inclisiran (n = 1,494) compared to placebo (n = 1,477) on MACEs within the ASCVD and ASCVD-RE populations is relevant.

The incidence of MACEs in the inclisiran and placebo arms of the ORION-9 trial were 10 (4.1%) and 10 (4.2%), respectively; the absolute number of MACEs for the inclisiran versus placebo arms were 10 and 11 events, respectively; [redacted].

The exploratory end point of nonfatal MI occurred in [redacted]

#### *Low-Density Lipoprotein Cholesterol*

The co-primary end points of percent change in LDL-C from baseline to day 510 and time-average percent change in LDL-C from baseline after day 90 and up to day 540 were the same for the ORION-9, ORION-10, and ORION-11 trials.

The between-group difference between inclisiran and placebo in percent reduction in LDL-C in the ORION-9 trial was −47.9% (95% CI, −53.5% to −42.3%; P < 0.0001). For the time-average percent change in LDL-C

from baseline after day 90 and up to day 540, the least squares mean difference versus placebo favoured inclisiran in the ORION-9 trial (−44.30%; 95% CI, −48.48% to −40.12%; P < 0.0001). The results of the sensitivity analyses for both outcomes were consistent with the overall population.

### Harms Results in Patients With HeFH

In the ORION-9 trial, the most common AEs in the inclisiran and placebo groups were nasopharyngitis (11.6% and 8.3%, respectively), influenza (5.4% and 8.8%), upper respiratory tract infection (6.6% and 6.7%), and back pain (7.1% and 4.2%). There were 18 patients (7.5%) in the inclisiran arm and 33 patients (13.8%) in the placebo arm who experienced at least 1 serious adverse event (SAE). The most common SAEs were unstable angina, myocardial ischemia, acute MI, aortic valve stenosis, and back pain. Three patients (1.2%) in the inclisiran group, and no patients in the placebo group, withdrew due to an AE. Reasons leading to withdrawal from the study drug were prostate cancer, injection site reaction, and rib fracture and cough, each in 1 patient. The cough and injection site reaction events were considered to be possibly related to treatment.

### Critical Appraisal

- There were a number of issues associated with the post hoc pooled analysis provided by the sponsor for this resubmission. First, it was a post hoc analysis, which increases the potential for bias. The primary analysis included all 3 pivotal trials (the ORION-9, ORION-10, and ORION-11 trials); however, this combined 2 separate populations of patients (patients with HeFH and patients with nFH with ASCVD), and these patients are being considered separately for this review. Importantly, the ORION-9, ORION-10, and ORION-11 trials were not powered to assess MACEs; the events were captured via the safety population and the definitions used may not have been sufficiently inclusive or specific; and there was no blinded, centralized assessment of events. Otherwise, the ORION-9, ORION-10, and ORION-11 trials appeared to have been reasonably well-conducted, with adequate measures to maintain blinding, a multiple testing procedure to reduce risk of type I error, and low dropout rates.
- With respect to external validity, key issues include the fact that clinical outcomes such as CV mortality and morbidity were not assessed in the pivotal ORION trials, and that there was no active comparator, such as PCSK9 monoclonal antibodies. Additionally, HRQoL was not assessed in any of the included trials.

## Long-Term Extension Studies: ORION-3 and ORION-8 Studies

### Description of Studies

The ORION-3 study was a 4-year, open-label extension study of the phase II ORION-1 trial. The primary objective of this study was to assess the effect of long-term treatment with twice-yearly small interfering RNA (siRNA) therapeutic inclisiran dosing on LDL-C reductions at day 210 compared to baseline in the ORION-1 trial. The secondary and exploratory objectives were to assess the effects of inclisiran on cholesterol and other lipid levels and PCSK9 levels up to 4 years in each arm, as well as the long-term safety and tolerability of inclisiran. Another exploratory objective was to evaluate the effects of transitioning from evolocumab to inclisiran. A total of 382 participants were enrolled from 52 centres across 5 countries, among them 56 patients enrolled from Canadian centres.

The ORION-8 trial is an ongoing, global, open-label, long-term extension study in individuals with ASCVD, ASCVD-RE, or HeFH and elevated LDL-C despite MTD of LDL-C–lowering therapies, who have completed the phase II ORION-3 study or any of the phase III ORION-9, ORION-10, or ORION-11 studies. The primary objectives of the study are to evaluate the effect of inclisiran treatment on the proportion of individuals meeting prespecified LDL-C targets, and the safety and tolerability of long-term use of inclisiran. The secondary objectives are to evaluate the effect of inclisiran on LDL-C levels and other lipids and lipoproteins. The study has enrolled 3,274 participants from 268 centres in 13 countries, including Canada (3 centres).

**Efficacy Results**

Of the original ORION-1 cohort of 497 patients, 290 of 370 patients allocated to the study drug continued into the inclisiran-only arm, and 92 of 127 patients allocated to placebo entered the switching arm in the ORION-3 extension study conducted between March 24, 2017, and December 17, 2021. Overall, efficacy results were consistent and sustained up to the end of the study. In the inclisiran-only arm, LDL-C was reduced by 47.5% (95% CI, 50.7% to 44.3%) at day 210 and sustained over 1,440 days. During the 4 years of open-label extension, the mean percentage change and mean absolute change in LDL-C concentrations in the inclisiran-only arm ranged between −34.3% and −53.8%, and −1.13 mmol/L to −1.76 mmol/L, respectively, with the upper limit of the 95% CI at all time points being lower than −30% and excluding zero. The mean percentage change and mean absolute change in LDL-C in the switching arm ranged between −38.2% and −65.7%, and between −1.20 mmol/L and −2.00 mmol/L, respectively.

In the inclisiran-only arm, the mean percentage change in total cholesterol ranged from −21.1% to −30.2%, remaining relatively consistent throughout the follow-up period. Non-HDL-C, Apo-B, and triglycerides also remained consistently decreased throughout the follow-up period. Lp(a) concentration decreased by 16.3% at day 30 with no meaningful changes thereafter.

In the ORION-8 study, the proportion of patients who reached global lipid targets at day 1,080 was similar in the inclisiran-only group (78%), the switching group (79%), and patients who rolled over from the ORION-3 trial (77%). The percentage of ASCVD patients who reached global lipid targets (< 70 mg/dL) at day 1,080 was also similar between the inclisiran-only group (79%), the switching group (80%), and those who rolled over from the ORION-3 trial (77%). The percentage of patients with ASCVD-RE who reached global lipid targets (< 100 mg/dL) was 73% in the inclisiran-only group, 75% in the switching group, and 77% in those who rolled over from the ORION-3 trial.

The mean percentage change from baseline to day 1,080 in LDL-C was −49.0% (95% CI, −50.5% to −47.4%) in the inclisiran-only group, −49.7% (95% CI, −51.3% to −48.0%) in the switching group, and −50.0% (95% CI, −52.6% to −47.3%) in the group that rolled over from the ORION-3 trial.

**Harms Results**

The most common AEs in the ORION-3 trial were infection, hypertension, arthralgia, and fatigue. In the inclisiran-only arm, 275 patients (96.8%) experienced at least 1 AE. A total of 104 patients (36.6%) experienced at least 1 SAE. Nineteen patients (6.7%) and 12 patients (4.2%) discontinued the study treatment due to AEs and SAEs, respectively.

Overall, out of 87 total patients in the switching arm, 80 patients (92%) experienced at least 1 AE and 30 patients (34.5%) experienced at least 1 SAE. Five patients (5.7%) and 3 patients (3.4%) discontinued the study treatment due to AEs and SAEs, respectively.

Over the 4-year study duration, 7 deaths (2.5%) were reported in the inclisiran arm and 1 death was reported in the switching arm; none of the deaths were assessed as drug-related.

In the ORION-8 study, 79% of patients in both the inclisiran-only arm and switching arm reported an AE, as well as 64% of patients who rolled over from the ORION-3 trial. There were also similar numbers of patients who discontinued treatment due to an AE ([redacted]) in the inclisiran-only arm andswitching arm, versus [redacted] of patients who rolled over from the ORION-3 trial.

With respect to SAEs, 31% of patients in the inclisiran-only group, 33% of patients in the switching group, and 15% of patients who rolled over from the ORION-3 trial experienced a SAE.

With respect to AE of special interest, the following occurred in the inclisiran-only group, the switching group, and the group that rolled over from the ORION-3 trial: [redacted]

[redacted]

### Critical Appraisal

The open-label design of the ORION-3 and ORION-8 studies is considered a limitation that could bias the result parameters. Furthermore, only those who completed the parent trials were eligible for participation into these extensions, which might have led to a selection bias. The lack of a control or comparator arm is considered a key constraint that limits the interpretation of study outcomes.

As the ORION-3 and ORION-8 studies consisted of patients who took part in the pivotal studies, it is reasonable to expect that the same strengths and limitations related to generalizability apply to the extension studies, with the additional caveat of potential selection bias due to the enrolment criteria.

## Indirect Comparisons

### Description of Studies

The sponsor submitted an ITC that compared the efficacy of inclisiran to relevant drug comparators in patients with HeFH or ASCVD (or ASCVD-RE). The objective of the sponsor-submitted report was to conduct a feasibility assessment via systematic review of the literature and, if possible, to conduct an indirect comparison evaluating the relative efficacy and safety of inclisiran versus relevant drug comparators including ezetimibe, and PCSK9 monoclonal antibodies in patients with HeFH or ASCVD (or ASCVD-RE).

The sponsor-submitted ITC was informed by a systematic review of RCTs conducted in April 2020. Thirty-nine studies met the inclusion criteria of the review and feasibility assessment, and 24 studies were subselected for inclusion in the ITC based on network connectivity and homogeneity in study characteristics, patient characteristics, or outcomes that were likely modifiers of the relative treatment effects.

The analyses were conducted using a network meta-analysis (NMA). Selection of both fixed and random effects were conducted for outcomes of interest. Random effects analyses were selected as the base case, given the number of studies per node and observed heterogeneity in patient and trial characteristics. Three network scenarios were conducted: patients with HeFH on MTD statins, patients with ASCVD and ASCVD-RE on MTD statins, and patients with ASCVD and ASCVD-RE who are intolerant to statins. Efficacy outcomes included percent, absolute, and time-adjusted change from baseline in LDL-C, and percent change from baseline in HDL-C, and safety outcomes included total discontinuations, and discontinuations due to AEs.

### Efficacy Results

A total of 7 trials were included in the network for the HeFH population on MTD statins; 13 studies were included in the base-case network for the ASCVD and ASCVD-RE populations on MTD statins, where 1 closed loop was formed; and 7 trials were included in the network for ASCVD and ASCVD-RE populations intolerant to statins. In the HeFH population on MTD statins, there was no difference between inclisiran and alirocumab or evolocumab for any efficacy and safety outcomes. In the network for the ASCVD and ASCVD-RE population on MTD statins, inclisiran was favoured over ezetimibe for efficacy outcomes related to LDL-C; however, there was no difference between inclisiran and alirocumab or evolocumab for any efficacy or safety outcomes. In the network for the ASCVD and ASCVD-RE population intolerant to statins, inclisiran was favoured over ezetimibe for efficacy outcomes related to LDL-C but not safety outcomes. There was no difference between inclisiran and alirocumab or evolocumab in any efficacy or safety outcomes.

### Critical Appraisal

There were several limitations with the key assumptions made in the NMA approach with regard to the background statin use and the time of assessment of outcomes, impacting clinical and methodological heterogeneity, which resulted in limited interpretability and generalizability of the results. Though not reported or accounted for, these assumptions likely impacted treatment effects and the results of each NMA, and were a significant source of heterogeneity in the studies. It was assumed in the NMA that individual statins had similar efficacy as background therapy regardless of dose and would not bias the results of the NMA; however, based on discussions with the clinical expert consulted by CADTH, this was not considered a reasonable assumption. It was also assumed that differences in CV risk and severity would not impact the relative effects on LDL-C; therefore, no attempt to adjust for differences in baseline characteristics was conducted due to the number of studies and inconsistent reporting of characteristics. The NMA used 24 weeks as the time of assessment, which was considered acceptable for lipid and lipoprotein outcomes. End-of-study values for safety were used and considered comparable if the duration of follow-up was 24 weeks or longer. Variations in trial length would likely influence the number of patients withdrawing for various reasons and, given the 24-week time of assessment, may have undermined true treatment effects. Additionally, given the biannual dosing regimen of inclisiran, a 24-week time of assessment may have been insufficient to assess safety outcomes compared to the every 2 weeks dosing regimen of alirocumab and evolocumab.

Overall, the studies included in the NMA were believed to be statistically heterogeneous based on the considerable $I^2$; however, it is unclear what the source of heterogeneity was. The observed heterogeneity was likely due to observed and unobserved differences in patient populations across the included studies, data

imputation analysis methods, and the specific background treatments allowed and/or delivered. Unidentified or unknown clinical (particularly treatment effect modifiers) or methodological heterogeneity need to be explored, as it is unclear if the transitivity assumption was appropriately met.

In general, all treatments were favoured over placebo for all outcomes in each network scenario; however, the results typically displayed exceedingly wide credible intervals (CrIs), challenging the precision of the results.

## Studies Addressing Gaps in the Evidence From the Systematic Review

### Pooled Safety Analysis of 7 ORION Trials

#### *Description of Studies*

This post hoc analysis comprised patients treated with 300 mg inclisiran sodium or placebo in the completed (ORION-1, ORION-3, ORION-5, ORION-9, ORION-10, and ORION-11) and ongoing (ORION-8) trials. The objective was to obtain data regarding the long-term safety and tolerability of inclisiran for up to 6 years in a large, pooled dataset from 7 completed and ongoing trials and diverse sample of patients at risk for CV events. Exposure-adjusted incidence rates and Kaplan-Meier estimates of cumulative incidence of reported treatment-emergent AEs, abnormal laboratory measurements, and incidence of antidrug antibodies (ADAs) were analyzed.

This analysis included 3,576 patients treated with inclisiran for up to 6 years and 1,968 patients treated with placebo for up to 1.5 years, with 9,982.1 and 2,647.7 patient-years of exposure, respectively.

#### *Harms Results*

At least 1 SAE was reported in 32.2% and 22.1% patients in the inclisiran and placebo groups, respectively. The most common SAEs were cardiac events, reported in 11.6% and 9.0% patients, respectively. At least 1 AE led to study drug discontinuation in 3.2% and 1.7% of patients in the inclisiran and placebo groups, respectively.

AEs at the injection site were more frequent with inclisiran (9.3%) than placebo (1.8%). AEs at the injection site leading to study drug discontinuation were higher with inclisiran (0.1 per 100 patient-years) than placebo (0.0 per 100 patient-years).

Kaplan-Meier analyses showed that AEs that were serious or led to discontinuation; hepatic, muscle, and kidney events; incident diabetes; and elevations of creatine kinase or creatinine accrued at a comparable rate between groups for up to 1.5 years, with similar trends continuing for inclisiran beyond this period. Fewer major CV events reported as AEs occurred with inclisiran during this period. Treatment-induced ADAs were uncommon with inclisiran (4.6%), with few of these being persistent (1.4%).

#### *Critical Appraisal*

##### Internal Validity

The findings were derived from pooled data from 7 clinical trials with specific inclusion criteria, and thus patient populations enrolled at different times may have had different clinical characteristics not reflected in the tables of baseline characteristics and may not be fully reflective of the general population. Although

exposure-adjusted incidence rates were calculated, no direct comparison of events with inclisiran versus placebo is possible beyond the first 1.5 years, and only a few patients were exposed to inclisiran for more than 4 years, which limits our ability to draw meaningful conclusions.

### External Validity

The pooled data analysis consisted of patients who took part in the pivotal studies; it is reasonable to expect that the same strengths and limitations related to generalizability apply to this study.

# Economic Evidence

## Cost and Cost-Effectiveness

### Table 3: Summary of Economic Evaluation

| Component | Description |
|---|---|
| **Type of economic evaluation** | Cost-minimization analysis |
| **Target population** | Adult patients with HeFH who require additional lowering of LDL-C despite maximally tolerated statin therapy |
| **Treatment** | Inclisiran plus SoC (defined as maximally tolerated dose of statin therapy, with or without ezetimibe) |
| **Dose regimen** | 284 mg initially, at month 3, and every 6 months thereafter |
| **Submitted price** | Inclisiran, 284 mg/1.5 mL, prefilled syringe: $2,839.28 |
| **Treatment cost** | $5,679 per year |
| **Comparators** | • Alirocumab<br>• Evolocumab (140 mg/mL)<br>• Evolocumab (120 mg/mL) |
| **Perspective** | Canadian publicly funded health care payer |
| **Time horizon** | 2, 4, 5, 10, 15, and 25 years |
| **Key data sources** | ORION-10 and ORION-11 trials, both randomized controlled trials vs. placebo<br>Sponsor-submitted NMA |
| **Key limitations** | • The relative clinical effectiveness of inclisiran is highly uncertain. While greater reductions in LDL-C may be achieved with inclisiran relative to SoC, there is no evidence to suggest that it is more effective than existing PCSK9 monoclonal antibodies. |
| **CADTH reanalysis results** | • CADTH did not undertake a reanalysis of the sponsor's base case.<br>• If patients are treated with inclisiran for more than 2 years, no price reduction is required compared to alirocumab or evolocumab at public list prices. |

HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; NMA = network meta-analysis; SOC = standard of care; vs. = versus.

## Budget Impact

CADTH identified the following key limitation with the sponsor's submitted budget impact analysis (BIA): the comparator prices were uncertain. In the absence of more reliable input values for the BIA, the sponsor's

base case was maintained. The budget impact of inclisiran was estimated to be $2,126,379 in year 1; $474,051 in year 2; and –$2,160,026 in year 3. The 3-year net budget impact was $440,404.

## Request for Reconsideration

The sponsor filed a request for reconsideration of the draft recommendation for inclisiran as an adjunct to lifestyle changes, including diet, to further reduce LDL-C levels in adults with HeFH who are on the MTD of a statin, with or without other LDL-C–lowering therapies. In their request, the sponsor identified the following issues:

- The sponsor was of the view that the CDEC draft recommendation not to reimburse was inconsistent with the evidence standard applied to all other reimbursed LDL-C–lowering therapies for HeFH, and clinical guidelines.
- The sponsor stated that the CDEC draft recommendation did not consider the pathophysiology of HeFH; HeFH is a genetic disease that results in reduced LDL-C clearance, thus making the lowering of LDL-C the only means to correct for the genetic basis disease and lower CV risk in these patients.
- The sponsor was of the view that the CDEC draft recommendation did not seem to adequately consider clinician input.

In the meeting to discuss the sponsor's request for reconsideration, CDEC considered the following information:

- information from the initial submission related to the issues identified by the sponsor
- feedback from 3 clinical specialists with expertise in the diagnosing and treating patients with HeFH
- feedback on the draft recommendation from 2 patient groups, the HeartLife Foundation and the CHPA
- feedback on the draft recommendation from 51 clinician groups: associate professors at the University of British Columbia; Cambridge PREVENT Clinic and Secondary Cardiac Rehab; Cape Breton Regional Hospital Cardiology; cardiologists from Kamloops; Cardiology Associates of Niagara; Cardiology Services Group, Belleville, Ontario; CardioPulmonary Services at the Boardwalk, Waterloo, Ontario; CCS Dyslipidemia Guidelines Committee; Circulate Cardiac and Vascular Care; Civic Heart Centre; Corcare Inc.; Diabetes Heart Research Centre; Dr. V. Sluzar Medicine Professional Corporation; Doclinic; Durham Care Clinic; Edmonton Cardiology Consultants; endocrinologists from Windsor; Edmonton Zone Cardiac Rehabilitation; Familial Hypercholesterolemia Canada; Family Medicine Clinic; Heart Care and IMCare; Heart Care Canada; Heart Health Institute; Horizon Health Network, the Moncton Hospital; Kawartha Cardiology Clinic; Lipid Clinic McMaster University and Hamilton Health Sciences; Main Street Health Centre; Manitoba Clinic; Markham Health Plex Medical Centre; McMaster University Secondary Cardiovascular Prevention Clinic; North Shore Heart Centre; North Shore Lipid Clinic and Internal Medicine; North York Cardiac Diagnostic Centre; North York General; Oakville Cardiologists; PACE Cardiology; physicians from the University of British Columbia; physician group from One Heart Care; physician group from One Heart Care; physicians from Dartmouth

General Hospital; physicians from the University of Calgary; Queen Elizabeth II Health Sciences Centre – interventional cardiologists; Riverside Cardiology and Diagnostic Imaging; Service de cardiologie, Centre hospitalier universitaire Dr-Georges-L.-Dumont; St. Thomas Elgin General Hospital; TotalCardiology; TotalCardiology Rehabilitation; University of Alberta Mazankowski Alberta Heart Institute; University of Toronto faculty and clinicians at St Michael's Hospital who are actively involved in the treatment of patients with HeFH; Victoria Lipid Clinic Society; and Western University, Division of Cardiology and Cardiac Rehabilitation and Secondary Prevention Program

- feedback on the draft recommendation from the public drug programs that participate in the CADTH review process
- feedback on the draft recommendation from the sponsor.

All stakeholder feedback received in response to the draft recommendation is available on the CADTH website.

# CDEC Information

## Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Edward Xie, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Trudy Huyghebaert, Dr. Danyaal Raza, and Dr. Peter Zed

**Initial meeting date**: February 29, 2024

**Regrets**: None

**Conflicts of interest**: None

**Reconsideration meeting date**: June 27, 2024

**Regrets**: One expert committee member did not attend.

**Conflicts of interest**: None

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**Redactions:** Confidential information in this document may be redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

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