



## CADTH Reimbursement Recommendation

# Inclisiran (Leqvio)

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

**Sponsor:** Novartis Pharmaceuticals Canada Inc.

**Final recommendation:** Do not reimburse



# Summary

## What Is the CADTH Reimbursement Recommendation for Leqvio?

CADTH recommends that Leqvio not 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 nonfamilial hypercholesterolemia (nFH) with atherosclerotic cardiovascular disease (ASCVD).

### Why Did CADTH Make This Recommendation?

- Evidence from 2 clinical trials showed that treatment with Leqvio lowered bad cholesterol (LDL-C) in adults with nFH with ASCVD who were already being treated with the highest possible dose of statins and in those who cannot tolerate treatment with statins.
- A post hoc pooled analysis of major adverse cardiovascular events (MACEs) from the ORION-10 and ORION-11 trials precluded the Canadian Drug Expert Committee (CDEC) from determining whether inclisiran reduces the risk of cardiovascular morbidity and death in adults with nFH with ASCVD.
- Patients identified a need for treatments that are less burdensome, can reduce bad cholesterol (LDL-C) and cardiovascular morbidity and death, and improve health-related quality of life (HRQoL); however, there was not enough evidence to show that Leqvio would reduce cardiovascular morbidity and death or improve HRQoL.

### Additional Information

#### What Is nFH With ASCVD?

ASCVD occurs when LDL-C builds up inside the arteries, which leads to hardening and narrowing of the arteries and reduced blood flow. In Canada, the 1-year incidence rate for ASCVD ranges between 7.2 and 8.8 per 1,000 person-years, and the 5-year prevalence of ASCVD ranges between 6.91% to 8.55% in adults. Severe outcomes of ASCVD may include heart attack, stroke, or death.

#### Unmet Needs in nFH With ASCVD

Statins are the standard treatment for lowering cholesterol, but statins alone may not help most patients with nFH with ASCVD reach target cholesterol levels. Some patients with nFH with ASCVD also cannot tolerate the side effects of statins. There is a need for more treatments that



# Summary

lower bad cholesterol and reduce cardiovascular morbidity and death in these patients.

## **How Much Does Leqvio Cost?**

Treatment with Leqvio is expected to cost approximately \$8,516 per patient in the first year of treatment and \$5,679 in subsequent years.

## Recommendation

CDEC recommends that inclisiran not be reimbursed as an adjunct to lifestyle changes, including diet, to further reduce LDL-C levels in adults with nFH with ASCVD who are on an MTD of a statin, with or without other LDL-C-lowering therapies.

## Rationale for the Recommendation

As outlined in the 2022 CDEC final recommendation for inclisiran, there were 2 phase III, double-blind randomized controlled trials (RCTs) (ORION-10, N = 1,561 and ORION-11, N = 1,617) that demonstrated that there was a statistically significant improvement compared with placebo in lowering LDL-C levels in adults with nFH with ASCVD who were receiving an MTD of a statin or who were statin intolerant. The between-group differences in percentage change in LDL-C from baseline to day 510 were  $-57.64$  (95% confidence interval [CI],  $-60.86$  to  $-54.43$ ) in ORION-10 and  $-53.5$  (95% CI,  $-56.66$  to  $-50.35$ ) in ORION-11 (both  $P < 0.0001$ ). However, clinically relevant cardiovascular-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 2 ongoing studies (ORION-4 and ORION-8) were expected to provide further evidence regarding the efficacy and safety of inclisiran in preventing pertinent clinical outcomes. As part of the evidence base for the resubmission, CDEC considered a post hoc pooled analysis of MACEs from the ORION-10 and ORION-11 trials, as well as 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 limitation to the pooled analysis of MACEs was that it was conducted post hoc and included exploratory outcomes, as previously noted. These limitations precluded CDEC from determining whether inclisiran reduces the risk of cardiovascular morbidity and mortality. The open-label extension studies, ORION-3 and ORION-8, each lacked a comparator group, and this also precluded CDEC from drawing any conclusions about the relative longer-term efficacy and safety of inclisiran versus placebo for these outcomes.

The 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 cardiovascular morbidity and mortality, have fewer side effects than existing treatments, and improve HRQoL. The ORION studies have demonstrated that inclisiran reduces LDL-C levels compared to placebo in patients with ASCVD. However, there is insufficient evidence to assess the clinical benefit of inclisiran in terms of reducing the risk of cardiovascular events, cardiovascular death, or all-cause mortality. While CDEC recognized that the biannual dosing regimen may provide patients with a more manageable administration schedule, no HRQoL data were included; therefore, the impact of inclisiran on HRQoL is unknown.

## Discussion Points

- CDEC discussed that the post hoc pooled analysis of MACEs from the ORION-10 and ORION-11 trials has significant methodological limitations. CDEC noted that the main issues with the sponsor-submitted post hoc pooled analysis of MACEs from the ORION-9, ORION-10, and ORION-11 trials is that MACEs and their components were only an exploratory outcome from these ORION trials, and it was a post hoc analysis. The fact that MACEs and their components were exploratory outcomes from these ORION trials also introduces the potential for bias. Sample sizes were not determined based on these outcomes, events were captured via the safety population, and definitions may not have been inclusive or specific enough; there was no blinded, centralized assessment of events, and the timing was likely insufficient to assess cardiovascular events. In addition, using a post hoc analysis introduces significant potential for bias, as an investigator may be biased by their ability to see the data when deciding what analyses to conduct and how to construct the composite outcome. Finally, combining results from all 3 ORION trials is inappropriate, as this ignores the fact that these trials feature 2 distinct populations, each separately identified within the indication. Additionally, there could have been issues with pooling the ORION-10 and ORION-11 trials, as there are some differences in baseline characteristics between these 2 study populations, most notably that all patients in the ORION-10 trial had ASCVD, while approximately 88% of patients in the ORION-11 trial had ASCVD, with the remaining categorized as ASCVD risk equivalent (RE). There was also a higher percentage of patients who discontinued treatment in the ORION-10 trial compared to the ORION-11 trial, further reinforcing that these are 2 distinct study populations. As a result, the ability to draw a conclusion on the effect of inclisiran on cardiovascular morbidity or mortality is limited.
- While CDEC recognized that there is a health need for patients who do not reach LDL-C targets despite available treatments and that reducing LDL-C levels is an important outcome in patients with ASCVD, it was noted that, while for many treatments there is evidence that lowering LDL-C levels correlates with a reduction in risk of cardiovascular events, extrapolation from other trials or to other populations based on LDL-C levels is not substantiated by the currently available evidence.
- CDEC discussed that the ORION-4 study, which was noted in the recommendation issued in 2022 as a potential source of data for cardiovascular morbidity and mortality, features a population with ASCVD and that it would provide further evidence to better characterize the efficacy and safety of inclisiran in preventing pertinent clinical outcomes, including a reduction in cardiovascular events, cardiovascular-related death, and all-cause mortality, and thus contribute valuable information regarding the long-term safety and efficacy of inclisiran; however, the ORION-4 study is still ongoing and was not submitted by the sponsor.
- In the recommendation issued for inclisiran in 2022, CDEC discussed that there is no evidence that inclisiran will be better tolerated in patients whose disease did not respond, or who were intolerant, to PCSK9 inhibitors. It also noted that the efficacy of switching from PCSK9 inhibitors to inclisiran on reduction in LDL-C levels and cardiovascular morbidity and mortality is unknown. CDEC discussed that no new evidence submitted by the sponsor changes this.

- Given that hypercholesterolemia requires lifelong treatment, CDEC noted at the time of the 2022 recommendation that there is uncertainty regarding the long-term efficacy and safety of inclisiran for the treatment of adults with nFH with ASCVD. CDEC also noted that the novel mechanism of action for inclisiran adds to the uncertainty. The ORION-3 (a 4-year open-label extension of the phase II ORION-1 trial) and ORION-8 (a 3-year open-label extension of the ORION-3 trial, as well as the ORION-9, ORION-10, and ORION-11 trials) long-term extension trials provided some evidence that the reductions in LDL-C levels seen in the ORION trials is durable and there was no evidence of new safety issues; however, any conclusions that can be drawn from these trials are limited by the lack of MACE outcomes, lack of a comparator group, and lack of blinding.
- In the 2022 recommendation issued for inclisiran, CDEC discussed the lack of direct comparative evidence for inclisiran versus the PCSK9 inhibitors or other add-on drugs such as ezetimibe. It 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 level reduction compared with evolocumab or alirocumab, although CDEC also noted uncertainty about the ITC results because of the inherent heterogeneity across the trials in the networks, and the fact 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) (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, 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 between 7.2 and 8.8 per 1,000 person-years, and the 5-year prevalence of ASCVD ranges between 6.91% and 8.55% in adults.

Elevated LDL-C levels are directly associated with the development of atherosclerosis and ASCVD. The 3 main subcategories of ASCVD are coronary artery disease, cerebrovascular disease, and peripheral arterial disease (PAD). Individuals with hypercholesterolemia and a history of an atherosclerotic event are categorized as having established clinical ASCVD (i.e., secondary prevention, which refers to the effort to treat known ASCVD and to prevent or delay the onset of disease manifestations), while individuals with hypercholesterolemia at risk of developing ASCVD need primary prevention (i.e., the effort to prevent or delay the onset of ASCVD). A subset of those needing primary prevention who are at greater risk of ASCVD are referred to as having ASCVD RE. Patient with ASCVD RE are defined as those with type 2 diabetes mellitus, FH, or a 10-year risk of a cardiovascular event of 20% or higher as assessed by the Framingham Risk Score for CVD or an equivalent. The proportion of the overall ASCVD population 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, these patients with high-risk nFH ASCVD are defined as those with any of the following criteria: diabetes, recurrent vascular events, PAD, or acute coronary syndrome in the past 12 months; and with LDL-C levels greater than 1.8 mmol/L despite MTD statins with or without other lipid-lowering therapies. Throughout this document, the high-risk ASCVD subgroup will refer 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 the LDL receptor, ApoB, 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 or heterozygous FH (HeFH). HeFH has an estimated prevalence of approximately 1 in 250 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 cardiovascular events compared with the general population.

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

- HeFH
- nFH with ASCVD.

Inclisiran is a double-stranded small interfering ribonucleic acid (RNA) that causes the degradation of PCSK9 messenger RNA. 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 followed by every 6 months.

## Submission History

Inclisiran was previously reviewed by CADTH in February 2022 for the same indication and the recommendation was to not reimburse. The key reasons for this recommendation were that there was insufficient evidence that inclisiran reduced cardiovascular morbidity and mortality, or all-cause mortality, as the pivotal trials, ORION 9, 10 and 11, were not designed to assess these outcomes. Additionally, CDEC noted that the long-term efficacy and safety of inclisiran have not been determined, and that there were 2 ongoing studies, ORION-4 and ORION-8, that were expected to provide further evidence to better characterize the pertinent clinical outcomes, as well as 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 drugs, and that there were limitations with the submitted ITC, including the relatively short follow-up (24 weeks) in a chronic condition.

The sponsor outlined the basis for their resubmission. In an effort to address the lack of evidence for reduction of cardiovascular morbidity and/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 submitted the findings of the long-term extensions, ORION-3 and ORION-8. To address the issue over lack of long-term safety data, in addition to ORION-3 and ORION-8, the sponsor submitted a pooled analysis of 7 ORION trials. Finally, the sponsor submitted a revised budget impact model to address CADTH's concerns in the first recommendation.

## Sources of Information Used by the Committee

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

- a review of 2 RCTs in adults with nFH with ASCVD
- a review of a post hoc pooled analysis of MACEs in the pivotal ORION studies
- a review of 2 long-term extension studies (ORION-3 and ORION-8)
- patients' perspectives gathered by patient groups, the Canadian Heart Patient Alliance (CHPA) and the HeartLife Foundation
- input from the public drug plans that participate in the CADTH review process
- 3 clinical specialists with expertise diagnosing and treating patients with HeFH and nFH with ASCVD
- input from 14 clinician groups, including Alberta Cardiovascular Disease Prevention Collaborative; BC Lipid specialists; CHU 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, 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 are 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, the CHPA and the HeartLife Foundation, provided input via a survey and interviews (CHPA) and from executives of the HeartLife Foundation.

Patients describe a condition that is very difficult to manage, impacts their physical and mental well-being, has a significant financial burden on families, and impacts patients' quality of life. Symptoms like shortness



of breath, chest pain, and fatigue were stated by the respondents who indicated 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 treatment, such as PCSK9 inhibitors, 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 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 the long-term health consequences by effectively managing LDL-C levels below the recommended threshold. 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

Barriers to adherence, intolerance to high-intensity statins, inability to reach recommended lipid targets despite an MTD of statin and ezetimibe, and lack of access to PCSK9 inhibitors are the major unmet needs identified by the clinical experts in the treatment of patients with HeFH and with nFH with ASCVD. Accordingly, the clinical experts noted that, in addition to being another PCSK9-targeting drug, inclisiran may help with barriers to adherence because of the less frequent dosing schedule.

The clinical experts indicated that, for patients with HeFH, in addition to those patients unable to reach LDL-C targets despite maximally tolerated statin, with or without ezetimibe, patients who would be especially well-suited would be those with other risk factors, such as smoking, diabetes, hypertension, or elevated lipoprotein (a). The clinical experts noted that patients with nFH with ASCVD who would be well-suited for Inclisiran would be those unable to tolerate high-intensity statins, those with early disease onset or recurrent disease, those whose LDL-C level is far from the threshold, and those with the risk factors identified for patients with HeFH. The clinical experts also referenced the 2021 CCS guidelines, which identified which patients in need of secondary prevention are likely derive the most benefit from intensification of statin therapy with the additional use of a PCSK9 inhibitor. This included patients with recent acute coronary syndrome (within 52 weeks), diabetes mellitus or metabolic syndrome, polyvascular disease, symptomatic PAD, recurrent myocardial infarction (MI), MI in the past 2 years, previous coronary artery bypass graft surgery, an LDL-C level of 2.6 mmol/L or greater or HeFH, or a lipoprotein (a) level of 120 nmol/L or greater.

The clinical experts noted that genetic testing should not be required to confirm a HeFH diagnosis because of lack of testing availability, 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 levels, including non-high-density lipoprotein cholesterol (HDL-C) and ApoB levels. 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: Alberta Cardiovascular Disease Prevention Collaborative (8 clinicians contributed to the input); BC Lipid Specialists (11 clinicians contributed to the input); CHU 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 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 (10 clinicians contributed to the input).

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

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

## 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 discontinuation of therapy.

## 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 adults with HeFH (the ORION-9 trial) or ASCVD (the ORION-10

and ORION-11 trials) and ASCVD RE (the ORION-11 trial) (i.e., those with diabetes, FH, or a 10-year risk of a cardiovascular event of  $\geq 20\%$  as assessed by the Framingham Risk Score for CVD or equivalent) who were receiving MTD statins or who were statin intolerant. Patients in the ORION-9 study had a history of HeFH with a diagnosis of HeFH by genetic testing or phenotypic Simon Broome criteria, and/or a documented history of an untreated LDL-C level of greater than 190 mg/dL, and a family history of FH (elevated cholesterol or early heart disease may indicate FH). In all 3 ORION studies, patients were randomized 1:1 to either inclisiran sodium 300 mg or placebo in addition to an MTD statin. The ORION-9, ORION-10, and ORION-11 trials enrolled 482, 1,561, 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 level from baseline to day 510. In all trials the coprimary 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 cardiovascular 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 was a secondary outcome reported as adverse events (AEs) in the ORION studies.

The 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% coronary heart disease). Approximately two-thirds of patients (69.4%) were on a high-intensity statins 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%). The patients were mostly males (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 nFH With ASCVD**

### ***Major Adverse Cardiovascular Events***

In the ORION-9, ORION-10, and ORION-11 trials, the exploratory end point of MACEs was defined as the composite of cardiovascular 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 HeFH and the nFH with ASCVD populations, 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.



### ***Low-Density Lipoprotein Cholesterol***

The coprimary end points of percent change in LDL-C level from baseline to day 510 and time-average percent change in LDL-C from baseline after day 90 and up to day 510 was 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-10 trial was  $-52.3\%$  (95% CI,  $-55.7$  to  $-48.8$ ;  $P < 0.0001$ ), and in the ORION-11 trial was  $-49.9\%$  (95% CI,  $-53.1$  to  $-46.6$ ;  $P < 0.0001$ ). For the time-average percent change in LDL-C level from baseline after day 90 and up to day 510, the least squares mean difference from placebo favoured inclisiran in the ORION-10 trial at  $-53.78\%$  (95% CI,  $-56.23$  to  $-51.33$ ) and the ORION-11 trial at  $-49.17\%$  (95% CI,  $-51.57$  to  $-46.77$ ) with all  $P < 0.0001$ . The results of the sensitivity analyses for both outcomes were consistent with the overall population.

### **Harms Results in Patients With nFH With ASCVD**

The frequency of AEs was consistent between patients treated with inclisiran and placebo, as well as across the trials, with patients experiencing at least 1 AE in 73.5% versus 74.8%, and 82.7% versus 81.5% in the ORION-10, and ORION-11 trials, respectively. In the ORION-10 and ORION-11 trials, serious adverse events (SAEs) occurred in 22.4% and 22.3% of patients treated with inclisiran compared to 26.3% and 22.5% of patients treated with placebo. Withdrawals due to AEs in the ORION-10 and ORION-11 trials were similar, with 2.4% and 2.8% of patients treated with inclisiran, respectively, and 2.2% of patients treated with placebo in both trials withdrawing due to AEs.

No difference in neurologic events and neurocognitive disorders was observed with inclisiran and placebo in any of the ORION trials; however, the frequency was higher in all placebo groups. In all trials, fewer patients treated with placebo reported AEs at the injection site than those treated with inclisiran. Injection-site reactions were mild to moderate, and no severe reactions were seen across the trials. There were no clear and consistent differences between inclisiran and placebo for other notable harms of hypersensitivity reactions, renal safety, or hepatic safety.

### **Critical Appraisal**

- There are a number of issues associated with the post hoc pooled analysis provided by the sponsor for this resubmission. First, it is a post hoc analysis, which increases the potential for bias. Their primary analysis includes all 3 pivotal trials (ORION-9 to ORION-11); however, this combines 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 to ORION-11 trials were not powered to assess MACEs – the events were captured via the safety population and the definitions used may not be inclusive or specific enough, and there was no blinded, centralized assessment of events. Otherwise, the ORION-9 to ORION-11 trials appear to have been reasonably well-conducted, with adequate measures to maintain blinding, a multiple testing procedure to reduce the risk of type I error, and low dropout rates.

- With respect to external validity, key issues are that clinical outcomes, such as cardiovascular mortality and morbidity, were not assessed in the pivotal ORION trials, and there was no active comparator, such as PCSK9 inhibitors. Additionally, HRQoL was not assessed in any of the included trials.

## Long-Term Extension Studies

### The ORION-3 and ORION-8 Studies

#### *Description of Studies*

The ORION-3 trial 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 therapeutic inclisiran dosing on LDL-C level 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 lipids 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 were enrolled from centres in Canada.

The ORION-8 trial is a global open-label, long-term extension study in those with ASCVD, ASCVD RE, or HeFH and elevated LDL-C levels, despite receiving an 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 patients achieving prespecified LDL-C level 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 [REDACTED]

#### *Efficacy Results*

Of the original ORION-1 cohort of 497 patients, 290 of 370 patients allocated to the 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 levels were 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 from -34.3% to -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 from -38.2% to -65.7% and -1.20 mmol/L to -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. Lipoprotein (a) concentration decreased by -16.3% at day 30 with no meaningful changes thereafter.

[REDACTED]

### **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, of a total of 87 patients in the switching arm, 80 patients (92%) experienced at least 1 AE. Thirty 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 group and 1 death in the switching arm, and none of the deaths was assessed as drug-related.

In the ORION-8 study, [REDACTED] of patients in each of the inclisiran-only and switching groups reported an AE, and [REDACTED] 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 group and the switching group, versus [REDACTED] of patients who rolled over from the ORION-3 trial.

With respect to SAEs, [REDACTED] of patients in the inclisiran-only group, [REDACTED] of patients in the switching group, and [REDACTED] of patients who rolled over from the ORION-3 trial experienced an SAE.

With respect to AEs of special interest, the following occurred in the inclisiran-only group, the switching group, and the group who rolled over from the ORION-3 study: [REDACTED]

[REDACTED]

[REDACTED]

### ***Critical Appraisal***

The open-label design of the ORION-3 and ORION-8 trials is considered a limitation that could bias the results parameters. Furthermore, only those who completed the parent trials were eligible for participation into these extensions, which might have led to selection bias. The lack of a control and/or comparator arm is considered a key constraint that limits the interpretation of the 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 other PCSK9 inhibitors 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 receiving an MTD statin, patients with ASCVD RE receiving an MTD statin, and patients with ASCVD RE who were intolerant to statins. The efficacy outcomes included percent, absolute, and time-adjusted change from baseline in LDL-C level, and percent change from baseline in HDL-C level; 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 receiving MTD statins, 13 studies were included in the base-case network for the ASCVD and RE populations receiving MTD statins, where 1 closed loop was formed, and 7 trials were included in the network for the ASCVD and RE populations who were intolerant to statins. In the HeFH population receiving MTD statins, there was no difference between inclisiran and alirocumab or evolocumab for any efficacy or safety outcomes. In the ASCVD and RE population receiving MTD statins, inclisiran was favoured over ezetimibe for efficacy outcomes related to LDL-C level; however, there was no difference between inclisiran and alirocumab or evolocumab for any efficacy or safety outcomes. In the ASCVD and RE population who were intolerant to statins, inclisiran was favoured over ezetimibe for efficacy outcomes related to LDL-C level 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 regards to background statin use and the time of outcomes assessment, which impacted clinical and methodological heterogeneity and 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 cardiovascular risk and severity would not impact the relative effects on LDL-C level, and therefore no attempt to adjust for differences in baseline characteristics was conducted because of 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 are bound to influence the number of patients withdrawing for various reasons and given the 24-week time of assessment, may undermine true treatment effects. Additionally, given the biannual dosing regimen of inclisiran, a 24-week time of assessment may be 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, the source of heterogeneity was unclear. The observed heterogeneity was likely because of 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, 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-8, 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 a diverse sample of patients at risk for cardiovascular 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 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% of patients in the inclisiran and placebo groups, respectively. The most common SAEs were cardiac, 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 with placebo (1.8%). AEs at the injection site leading to study drug discontinuation were higher with inclisiran (0.1 per 100 patient-years) than with placebo (0.0 per 100 patient-years).

Kaplan-Meier analyses showed that AEs that were serious or led to discontinuation (i.e., 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 cardiovascular events reported as AEs occurred with inclisiran during this period. Treatment-induced antidrug antibodies were uncommon with inclisiran (4.6%), with few of these persistent (1.4%).

### ***Critical Appraisal***

#### **Internal Validity**

The findings are derived from pooled data from 7 clinical trials with specific inclusion criteria; 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 a 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 drawing a meaningful conclusion.

#### **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 1: Summary of Economic Evaluation**

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adults with nFH with ASCVD who require additional lowering of LDL-C despite maximally tolerated statin therapy
Treatment	Inclisiran + SOC (defined as a maximally tolerated dose of statin therapy ± 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	Standard of care
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (40 years)
Key data sources	ORION-10, ORION-11, both randomized controlled trials vs. placebo Sponsor-submitted NMA
Key limitations	<ul style="list-style-type: none"> <li>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 inhibitors. Conclusions for the MACEs outcome could not be drawn due to a high risk of bias in the submitted analysis.</li> <li>The baseline risk of cardiovascular events may not reflect that of the population in Canada given the lack of Canadian-specific data.</li> <li>The sponsor’s probabilistic analysis did not specify any uncertainty with respect to baseline age, baseline LDL-C, sex, and diabetic status.</li> </ul>
CADTH reanalysis results	<ul style="list-style-type: none"> <li>The CADTH base case characterized the uncertainty in 4 input parameters in the probabilistic analysis: baseline age, baseline LDL-C, sex, and diabetic status.</li> <li>ICER = \$77,705 per QALY gained (incremental costs = \$59,990; incremental QALYs = 0.77)</li> <li>A 32% price reduction is required to be considered cost-effective at a willingness-to-pay threshold of \$50,000 per QALY gained.</li> </ul>

ASCVD = atherosclerotic cardiovascular disease; ICER = incremental cost-effectiveness ratio; LDL-c = low-density lipoprotein cholesterol; LY = life-year; MACE = major adverse cardiovascular events; nFH = nonfamilial hypercholesterolemia; NMA = network meta-analysis; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.

### Budget Impact

CADTH identified the following key limitation with the sponsor’s submitted budget impact analysis – the comparator prices are uncertain. In the absence of more reliable input values for the budget impact analysis, the sponsor’s base case was maintained. The net budget impact of inclisiran was estimated to be



\$344,838,487 in year 1, \$676,139,138 in year 2, and \$826,213,367 in year 3. The 3-year net budget impact was \$1,847,190,991.

## 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

**Meeting date:** February 29, 2024

**Regrets:** None

**Conflicts of interest:** None



**ISSN:** 2563-6596

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**Funding:** CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.