CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

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.

Recommendation: Reimburse with Conditions

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Recommendation

The CADTH 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 maximally tolerated dose 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 was one phase III, double-blind randomized controlled trial (RCT) (ORION-9, N=482) that demonstrated that there was a statistically significant improvement compared with placebo in lowering LDL-C levels in adult patients with HeFH who were receiving maximally tolerated dose of a statin or who were statin intolerant, the between-group differences 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-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 requires further review, and there is an ongoing study (ORION-8) that was expected to provide further evidence regarding the longer-term efficacy and safety of inclisiran in preventing pertinent clinical outcomes, with a subgroup of patients with HeFH. 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 seven 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 cardiovascular 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 cardiovascular morbidity and mortality, have fewer side effects than existing therapies, and improve health related quality of life. 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 bi-annual dosing regimen may provide patients with a more manageable administration schedule, though no health-related quality of life (HRQoL) data were included in the trials data to specifically address this.

At the sponsor submitted price for inclisiran and publicly listed price 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 proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor reimbursed for adults with HeFH who are on a maximally tolerated dose 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 inhibitors (i.e. alirocumab and evolocumab) currently reimbursed to reduce LDL-C level 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 inhibitors (i.e. alirocumab and evolocumab) currently reimbursed when considering initiation, renewal, and prescribing. The clinical expert noted that the place in therapy for inclisiran is comparable to that of the PCSK9 inhibitors (i.e. alirocumab and evolocumab).	
2. Inclisiran should not be reimbursed when used in combination with PCSK9 inhibitors	There is no evidence to support the use of inclisiran in combination with PCSK9 inhibitors.	
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 other PCSK9 inhibitors (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; PCSK9 = proprotein convertase subtilisin/kexin type 9.

Discussion Points

- The sponsor requested a reconsideration of the initial CDEC draft recommendation to not reimburse inclisiran 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. There were 3 issues outlined by the sponsor in the request for reconsideration that were discussed by CDEC. The first issue was the sponsor is of the view that CDEC draft recommendation not to reimburse is inconsistent with the evidence standard applied to all other reimbursed LDL-C lowering therapies for HeFH, clinical guidelines and other HTA appraisals for inclisiran. In the second issue the sponsor stated that CDEC draft recommendation does not consider the pathophysiology of HeFH. In the third issue the sponsor was of the view that CDEC draft recommendation does not seem to adequately consider clinician input.
- During the initial meeting, CDEC discussed that ORION-9 is the only pivotal ORION trial that included an HeFH population, therefore none of the pooled analyses submitted by the sponsor are relevant for the HeFH indication. The incidence of major adverse cardiac events (MACE) in ORION-9 was similar between inclisiran (4.1% of patients) and placebo (4.2% of patients) groups, therefore there is no evidence that inclisiran reduces the risk of cardiovascular 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, who suggested that due to the natural course of HeFH and the fact that there has never been a trial performed of adequate duration and size with any PCSK9 inhibitors to reveal differences between PCSK9 inhibitors and placebo for clinical outcomes such as cardiovascular morbidity and mortality and thus unlikely one will be done with inclisiran.

- CDEC discussed the post hoc pooled analysis of MACE events from the ORION-9, -10, and -11 trials submitted by the sponsor. However, they noted that the analysis has some limitations and potential biases. The primary issue is that MACE and its components were only an exploratory outcome. Sample sizes were not determined based on these outcomes, and definitions may not be 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 HeFH and nFH with ASCVD populations, as was done with ORION-9, 10 and 11. Moreover, the post-hoc analysis of MACE in ORION-9 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 cardiovascular events, and hence CDEC recognized that reducing LDL-C levels is an important outcome in patients with HeFH. 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 HeFH.
- 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 while it is unlikely to be relevant for the HeFH population, it would provide further evidence to better characterize the efficacy and safety of inclisiran in preventing pertinent clinical outcomes, including the reduction of cardiovascular events, cardiovascular-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 discussed that there is no evidence that inclisiran will be better tolerated in patients who did not respond or were intolerant to PCSK9 inhibitors and 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 there is no new evidence submitted by the sponsor that changes this.
- Given that hypercholesterolemia requires lifelong treatment, CDEC noted at the time of the recommendation that was issued in 2022 that there is 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 adds to the uncertainty. The ORION-3 (4-year open label extension of the phase 2 ORION-1 trial) and ORION-8 (3-year open label extension of the ORION-3 trial as well as ORION-9, ORION-10 and ORION-11) long term extension trials provided some evidence that the reductions in LDL-C 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 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 the PCSK9 inhibitors or other add-on agents such as ezetimibe. They noted that one sponsor-submitted indirect treatment comparison (ITC) suggested that inclisiran does not have a consistent nor distinct difference in efficacy in LDL-C reduction compared with evolocumab or alirocumab, although they also noted uncertainty about the ITC results due to the inherent heterogeneity across 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 one pre-requisite for atherosclerotic plaque development is the presence of low density lipoprotein cholesterol (LDL-C). Hypercholesterolemia can be grouped into two forms: non-familial hypercholesterolemia (nFH) and familial hypercholesterolemia (FH, also referred to as acquired or genetic hypercholesterolemia). Non-familial hypercholesterolemia 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 one year incidence rate for atherosclerotic cardiovascular disease (ASCVD) ranges between 7.2- 8.8 per 1000 person years, and the 5 year prevalence of ASCVD ranges between 6.91%- 8.55% in adults.

Elevated LDL-C is directly associated with the development of atherosclerosis and ASCVD. The three main subcategories of ASCVD are coronary artery disease (CAD), 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., they are secondary prevention patients), while individuals with hypercholesterolemia at risk of developing ASCVD are considered as primary prevention patients. A subset of primary prevention patients at greater risk of ASCVD are referred to as having an ASCVD risk-equivalent (ASCVD-RE). Patient with ASCVD-RE are defined as those with type 2 diabetes mellitus, FH, or with a 10-year risk of a CV event of ≥20% as assessed by the Framingham Risk Score (FRS) for CVD or 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 Canadian clinicians, these high-risk nFH ASCVD patients are defined as patients with any of the following criteria: a) diabetes, b) recurrent vascular events, c) peripheral arterial disease (PAD) or d) acute coronary syndrome (ACS) in the past 12 months; and with LDL-C levels >1.8 mmol/L despite maximally tolerated dose (MTD) statins with or without other lipid lowering therapies (LLTs). Throughout this document, the high-risk ASCVD subgroup will refer to patients with any of these criteria.

FH is one of the most common genetic disorders and is caused by mutations in the genes encoding LDL receptor (LDLR), apolipoprotein B (Apo-B), or proprotein convertase subtilisin/kexin type 9 (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 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 with the general population.

Inclisiran has a Health Canada indication as an adjunct to lifestyle changes, including diet, to further reduce low-density lipoprotein cholesterol (LDL-C) level in adults with the following conditions who are on maximally tolerated dose of a statin, with or without other LDL-C -lowering therapies:

- Heterozygous familial hypercholesterolemia (HeFH), or
- Non-familial hypercholesterolemia with atherosclerotic cardiovascular disease.

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 pre-filled 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. Key reasons for this recommendation included the fact that there was insufficient evidence 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 has not been determined, and that there were two ongoing studies, ORION-4 and ORION-8 that are 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 agents, and that there were limitations with the submitted indirect treatment comparison (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 CV morbidity/mortality and all-cause mortality, the sponsor included a post hoc pooled analysis of major adverse cardiovascular events (MACE) in the pivotal ORION studies, and to address concerns over long term efficacy and harms, 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 -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 1 RCT in adult patients with HeFH
- a review of post hoc pooled analysis of major adverse cardiovascular events (MACE) 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 public drug programs that participate in the CADTH review process
- Three of clinical specialists with expertise diagnosing and treating patients with HeFH and nFH with ASCVD
- input from 13 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 atherosclerotic cardiovascular disease and/or lipid disorders.
- a review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

Two patient groups, the Canadian Heart Patient Alliance (CHPA) and the HeartLife Foundation provided input via survey and interviews (CHPA) and by executives of the HeartLife Foundation.

Patients describe a condition that is very difficult to manage, impacts their physical and mental well-being, and has a significant financial burden on families and impacts their 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 the 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

Non-adherence, intolerance to high intensity statins, inability to reach recommended lipid targets despite MTD of statin and ezetimibe, and lack of access to PCSK9 inhibitors are the major unmet needs identified by the clinical experts in treatment of patients with HeFH and with nFH with ASCVD. Accordingly, the clinical experts believed that in addition to being another PCSK9-targeting drug, inclisiran may help with non-adherence 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 target despite maximally tolerated statin, with or without ezetimibe, patients who would be especially well-suited would include patients 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 threshold, and those with the risk factors identified for patients with HeFH. The clinical experts also referenced the 2021 CCS guidelines, which identified which secondary prevention patients are likely derive the most benefit from intensification of statin therapy with the additional use of a PCSK9 inhibitor. These included patients with recent ACS (within 52 weeks), diabetes mellitus or metabolic syndrome, polyvascular disease, symptomatic PAD, recurrent MI, MI in the past 2 years, previous CABG, 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 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 (HDL-C) and ApoB. 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

There were 13 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 (CHUDGLD; 6 clinicians contributed to the input), Cambridge Cardiac Rehab Program (6 clinicians contributed to the input), Canadian Cardiovascular Society (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 (STEGH; 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 atherosclerotic cardiovascular disease and/or lipid disorders.

The clinician groups agreed that the major issues with managing hypercholesterolemia, whether it be in HeFH or nFH patients with ASCVD, are adherence (as well as 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 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 struggle with adherence or tolerability.

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	
Orion-9, Orion-10, and Orion-11 were all placebo-controlled. 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 determine 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 jurisdications, 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 similar manner before initiating inclisiran?	The clinical experts noted to CDEC that a new criteria that have emerged in the past 3 years, based on work performed by Canadian researchers which indicate that a diagnosis of FH should be considered in patients with a baseline LDL-C of 5 mmol/L or greater for patients who are at least 40 years of age (or LDL-C ≥ 4.0 mmol/L for age < 18 years, or LDL-C ≥ 4.5 mmol/L for age ≥ 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 guidelines committees.
inclisiran is to be used as adjunct to maximally tolerated dose of a statin • what if the patient is statin intolerant? Would inclisiran be used as monotherapy? • For how long would maximally tolerated dose of a statin be used before adding inclisiran? • Does statin intensity matter (any statin vs. high-intensity statin)?	The clinical experts agreed that inclisiran could be used as monotherapy if a patient is intolerant to statins. The clinical experts noted that the length of trial of statin before moving to inclisiran is somewhat arbitrary, however 3 months would be a reasonable estimate. With respect to the question about whether statin intensity matters, the clinical experts noted that new data suggests that the better approach may be to use a moderate intensity statin along with ezetimibe, rather

Implementation issues	Response
• In the trials, patients not receiving 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? • There is a discrepancy in the definition of adherence to MTD of statins used by jurisdictions. What is considered "adherent" to MTD statins?	than pushing for a maximum tolerated dose of 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 doubling the statin dose and adding ezetimibe is unlikely going to be sufficient to achieve their target LDL-C. Yes, the clinical experts believed that patients trialing 2 different statins would be reasonable, and this is widely accepted. For MTD the clinical experts believed that one needs to rely on patient testimony when it comes to intolerance, and adherence is essentially defined as whether the patient is taking the drug, yes or no. CDEC recommended that inclisiran should be based on the criteria used by each of the public drug programs for initiation, renewal, and prescribing of the PCSK9 inhibitors (i.e. alirocumab and evolocumab) currently reimbursed to reduce LDL-C level in adults with HeFH. CDEC also noted that MTD should align with what was used in the trials and that a maximally tolerated dose of statins, and not a moderate intensity approach, should be implemented.
Should ezetimibe or other non-statin lipid-lowering therapies be used before starting inclisiran?	Reflecting the Canadian Cardiovascular Society 2021 guidelines, If a little above threshold (LDL-C 1.8 to 2.2 mmol/L), then yes adding ezetimibe makes sense according to the clinical experts, however if more than that (LDL-C of >2.2 mmol/L for example) then the ezetimibe step is a waste of time. The clinical experts believed that other LLT 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 inhibitors for the treatment of HeFH. For example: • confirmed adherence to high dose statin (e.g., atorvastatin 80mg or rosuvastatin 40mg) in combination with ezetimibe for at least a total of 3 months; OR • confirmed adherence to ezetimibe for at least a total of 3 months and inability to tolerate high dose statin. 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. CDEC recommended that inclisiran should be based on the criteria used by each of the public drug programs for initiation, renewal, and prescribing of the PCSK9 inhibitors (i.e. alirocumab and evolocumab) currently reimbursed to reduce LDL-C level in adults with HeFH.
Should the initiation criteria of inclisiran be aligned with that of alirocumab and evolocumab in patients with HeFH?	CDEC and the clinical experts agreed that the initiation criteria of 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 of inclisiran be aligned with that of alirocumab and evolocumab in patients with HeFH? Note: while CADTH recommendations for alirocumab and evolocumab does not include renewal criteria, some of the 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 do not align. 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

Implementation issues	Response
	not based on evidence, the more important target is for the patient to be reaching their targets for LDL-C. CDEC recommended that inclisiran should be based on the criteria used by each of the public drug programs for renewal of the PCSK9 inhibitors (i.e. alirocumab and evolocumab) currently reimbursed to reduce LDL-C level in adults with HeFH.
Considerations for discontinuation of therapy	
if a patient using inclisiran for primary prevention experiences a heart attack or stroke, should such 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 of inclisiran be aligned with that of alirocumab and evolocumab in patients with HeFH? Note: while CADTH recommendations for alirocumab and evolocumab does not include discontinuation criteria, some of the jurisdictions do have discontinuation criteria	The clinical experts stated that patients non responding should have the drug discontinued, however non-response to PCSK9 inhibitors is rare. In most cases, non-response is usually due to administration error. 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. CDEC recommended that inclisiran should be based on the criteria used by each of the public drug programs for discontinuation of the PCSK9 inhibitors (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; HeFH = heterozygous familial hypercholesterolemia; LDL-C low-density lipoprotein cholesterol; Lp(a)=lipoprotein a; MI = myocardial infarction; MTD = maximally tolerated dose; PAD = peripheral artery disease; PCSK9=proprotein convertase subtilisin\kexin type 9

Clinical Evidence

Systematic Review

Description of Studies

The major focus of this resubmission was a post hoc pooled analysis of MACE from the ORION-9, -10, and -11 trials. These trials, all included in the original submission, were phase III, double-blind, randomized controlled trials (RCTs) comparing inclisiran to placebo in adult patients with HeFH (ORION-9) or ASCVD (ORION-10 and -11) and ASCVD risk equivalent (ORION-11) [i.e., those with diabetes, FH or a 10-year risk of a CV event of ≥20% as assessed by the Framingham Risk Score for Cardiovascular Disease or equivalent]) who were receiving MTD statins, or who were statin intolerant. Patients in the ORION-9 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 of >190 mg/dL, and a family history of FH, elevated cholesterol or early heart disease may indicate FH. In all three ORION studies, patients were randomized 1:1 to either inclisiran sodium 300 mg or placebo in addition to MTD statin. The ORION-9, -10, and -11 trials enrolled 482, 1561, and 1617 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, -10, and -11 trials was the percent change in LDL-C from baseline to Day 510. In all trials the co-primary endpoint 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, non-fatal myocardial infarction (MI), non-fatal stroke (ischemic and hemorrhagic) were exploratory outcomes in the ORION trials within the composite outcome of MACE, and total deaths was a secondary outcomes reported as adverse events (AEs) in the ORION studies.

Baseline characteristics of the ORION trials were balanced between groups, and generally applicable to the Canadian population. 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% CHD). 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 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 HeFH

MACE

In the ORION-9, -10, and -11 trials, the exploratory endpoint of MACE was defined as the composite of CV death, cardiac arrest, non-fatal MI, and non-fatal stroke (haemorrhagic or non-haemorrhagic) using pre-defined 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, -10, and -11 trials and they also provided what they referred to as a sensitivity analysis that pooled data from the ORION-10 and -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 two 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=1494) compared to placebo (n=1477) on MACE within the ASCVD and ASCVD-RE populations is relevant.

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

The exploratory endpoint of non-fatal myocardial infarction occurred in [redacted]

LDL-C

The co-primary endpoints 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 three trials ORION-9, ORION-10, and ORION-11.

The between-group difference between inclisiran and placebo in percent reduction in LDL-C in ORION-9 was -47.9% (95% CI: -53.5, -42.3), p<0.0001. For the time-average percent change in LDL-C from baseline after Day 90 and up to Day 540 LSM difference from placebo favoured inclisiran in ORION-9: −44.30% (95% CI: −48.48, −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 ORION-9, the most common adverse events (AEs) in the inclisiran and placebo groups were nasopharyngitis (11.6% vs. 8.3%), influenza (5.4% vs. 8.8%), upper respiratory tract infection (6.6% vs. 6.7%), and back pain (7.1% vs. 4.2%). There were 18 (7.5%) of patients in the inclisiran arm and 33 (13.8%) of patients in the placebo arm who experienced at least one serious adverse event (SAE). The most common SAEs were unstable angina, myocardial ischaemia, acute MI, aortic valve stenosis, and back pain. Three (1.2%) patients in the inclisiran group withdrew due to an AE and no patients in the placebo group. Reasons leading to withdrawal from study drug were prostate cancer, injection site reaction, and rib fracture and cough, each in one patient. Cough and the injection site reaction events were considered possibility related to treatment.

Critical Appraisal

- There are a number of issues associated with the post hoc pooled analysis provided by the sponsor for this resubmission. First of all, it is a post hoc analysis, which increases the potential for bias. Their primary analysis includes all three pivotal trials (ORION-9 to -11), however this combines two 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 -11 trials were not powered to assess MACE, 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 -11 trials appear to have been reasonably well-conducted, with adequate measures to maintain blinding, a multiple testing procedure to reduce risk of type 1 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 the PCSK9 inhibitors. Additionally, health-related quality of life (HRQOL) was not assessed in any of the included trials.

Long-Term Extension Studies

ORION-3 and ORION-8

Description of Studies

ORION-3 was a 4-year open-label extension study of the phase 2 ORION-1 trial. The primary objective of this study was to assess the effect of long-term treatment with twice-yearly siRNA therapeutic inclisiran dosing on LDL-C reductions at day 210 compared to baseline in ORION-1. 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 Canadian centres.

ORION-8 is a global open-label, long-term extension study in subjects 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 subjects achieving 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 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 Dec 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 1440 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% 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 between -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. Lp(a) concentration decreased by -16.3% at day 30 with no meaningful changes thereafter.

In ORION-8, the proportion of patients who attained global lipid targets at day 1080 was similar between the inclisiran-only group (78%), the switching group (79%), and patients who rolled over from ORION-3 (77%). Similarly, the percent of ASCVD patients who attained global lipid targets (<70 mg/dL) at day 1080 was similar between the inclisiran-only group (79%), the switching group (80%), and those who were rolled over from ORION-3 (77%). The percent of patients with ASCVD RE who attained global lipid targets

(<100 mg/dL) was 73% in the inclisiran-only group, 75% of patients in the switching group, and 77% in those patients who were rolled over from ORION-3.

The mean percentage change from baseline to day 1080 in LDL-C was -49.0% (95% CI: -50.5, -47.4) in the inclisiran-only group, -49.7% (95% CI: -51.3, -48.0) in the switching group, and -50.0 (95% CI: -52.6, -47.3) in the group rolled over from ORION-3.

Harms Results

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

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

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

In ORION-8, 79% of patients in each of the inclisiran-only and switching groups reported an AE, and 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 group and the switching group, versus [redacted] of patients who rolled over from the ORION-3 trial.

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

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

[redacted]

Critical Appraisal

The open-label design of ORION-3 and ORION-8 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 potentially led to a selection bias. The lack of a control/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 enrollment 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 vs 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: HeFH patients on MTD statin, ASCVD and risk equivalent patients on MTD statin, and ASCVD and risk equivalent patients 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 seven 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 risk equivalent populations on MTD statins, where one closed loop was formed, and seven trials were included in the network for ASCVD and risk equivalent 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 ASCVD and risk equivalent population on MTD statin network, 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 ASCVD and risk equivalent population intolerant to statin network, 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 regards 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, and 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 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 Q2W 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 Seven ORION Trials

Description of Studies

This post hoc analysis comprised patients treated with 300 mg inclisiran sodium or placebo in the completed (ORION-1, -3, -5, -9, -10, and -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 seven 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 AE, abnormal laboratory measurements, and incidence of antidrug antibodies (ADA) were analyzed.

This analysis included 3576 patients treated with inclisiran for up to 6 years and 1968 patients treated with placebo for up to 1.5 years, with 9982.1 and 2647.7 patient-years of exposure, respectively.

Harms Results

At least one SAE was reported in 32.2% and 22.1% 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 one 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%) compared with placebo (1.8%) groups. AEs at the injection site leading to study drug discontinuation were higher on inclisiran (0.1 per 100 patient-years) than on 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 cardiovascular events reported as AEs occurred with inclisiran during this period. Treatment-induced ADA 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 seven 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 a general population. Although EAIRs 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 us to 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 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 + standard of care (SoC, defined as 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, pre-filled syringe: $2,839.28
Treatment Cost	$5,679 per year
Comparators	• Alirocumab • Evolocumab (140 mg / mL) • Evolocumab (120 mg / mL)
Perspective	Canadian publicly funded health care payer
Time horizon	2, 4, 5, 10, 15, & 25 years
Key data sources	ORION-10, ORION-11, both randomized controlled trials versus placebo 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 inhibitors.
CADTH reanalysis results	• CADTH did not undertake a reanalysis of the sponsor's base case. • If patients are treated with inclisiran for more than two 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.

Budget Impact

CADTH identified the following key limitations with the sponsor's submitted BIA: the comparator prices are 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 three-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 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. In their request, the sponsor identified the following issues:

- The sponsor is of the view that CDEC draft recommendation not to reimburse is inconsistent with the evidence standard applied to all other reimbursed LDL-C lowering therapies for HeFH, clinical guidelines and other HTA appraisals for inclisiran.
- The sponsor stated that CDEC draft recommendation does 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 is of the view that CDEC draft recommendation does 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 three clinical specialists with expertise in the diagnosing and treating patients with HeFH
- feedback on the draft recommendation from 2 patient groups, the HeartLife and the Canadian Heart Patient Alliance (CHPA)
- feedback on the draft recommendation from 51 clinician groups, Associate Professor at University of British Columbia; Cambridge PREVENT Clinic & Secondary Cardiac Rehab; Cape Breton Regional Hospital Cardiology; Cardiologist 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; Endocrinologist 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 Center; 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 Center; North York General; Oakville Cardiologists; PACE Cardiology; Physician from University of British Columbia; Physician group from One Heart Care; Physician group from One Heart Care; Physicians from Dartmouth General Hospital; Physicians from University of Calgary; Queen Elizabeth II Health Sciences Centre – Interventional cardiologists; Riverside Cardiology and Diagnostic Imaging; Service of cardiologie, CHU Dr-Georges-L-Dumont; St. Thomas Elgin General Hopsital (STEGH); 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 heterozygous familial hypercholesterolemia (HeFH); Victoria Lipid Clinic Society; 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