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CADTH Reimbursement Recommendation

Inclisiran (Leqvio)

Indication: As an adjunct to lifestyle changes, including diet, to further reduce low-density lipoprotein cholesterol (LDL-C) level in adults with 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.

Sponsor: Novartis Pharmaceuticals Canada Inc.

Final recommendation: Do not reimburse

CADTH

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Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Leqvio?

CADTH recommends that Leqvio should 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 of a statin, with or without other LDL-C–lowering therapies, and who have heterozygous familial hypercholesterolemia (HeFH) or non-familial hypercholesterolemia (nFH) with atherosclerotic cardiovascular disease (ASCVD).

Why Did CADTH Make This Recommendation?

- Evidence from 3 clinical trials showed that treatment with Leqvio lowered bad cholesterol (LDL-C) in adults with HeFH or nFH with ASCVD who were already being treated with the highest possible dose of statins and in those who cannot tolerate treatment with statins.
- Patients identified a need for treatments that can reduce bad cholesterol (LDL-C) and cardiovascular morbidity and death; however, there was not enough evidence to show that Leqvio would reduce cardiovascular morbidity and death. Results from 2 ongoing studies (ORION-4 and ORION-8) will contribute valuable information regarding the long-term safety and efficacy of Leqvio when results become available.

Additional Information

What Is HeFH or nFH With ASCVD?

Heterozygous familial hypercholesterolemia is a genetic disease that causes high cholesterol. Atherosclerotic cardiovascular disease occurs when LDL-C builds up inside the arteries leading to hardening and narrowing of arteries resulting in reduced blood flow. In Canada, an estimated 1 in 311 people are affected by HeFH, with approximately 145,000 patients currently living with HeFH. The number of people with ASCVD in Canada remains unknown, although ASCVD is the leading cause of death around the world with 17.9 million deaths each year. Severe outcomes of ASCVD may include heart attack, stroke, or death.

Unmet Needs in HeFH or nFH With ASCVD

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

How Much Does Leqvio Cost?

Treatment with Leqvio is expected to cost the public drug plans approximately $8,518 per patient in the first year of treatment and $5,679 per patient per year thereafter.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that inclisiran should not be reimbursed as an adjunct to lifestyle changes, including diet, to further reduce low-density lipoprotein cholesterol (LDL-C) level in adults with either of the following conditions who are on a maximally tolerated dose of a statin with or without other LDL-C–lowering therapies:

- heterozygous familial hypercholesterolemia (HeFH)
- non-familial hypercholesterolemia (nFH) with atherosclerotic cardiovascular disease (ASCVD).

Rationale for the Recommendation

Three double-blind, randomized controlled trials (RCTs) (ORION-9, ORION-10, and ORION-11) demonstrated that inclisiran 284 mg was associated with statistically significant improvements compared with placebo in lowering LDL-C levels in adult patients with HeFH or nFH with ASCVD who were receiving maximally tolerated dose of a statin or were statin intolerant; the between-group differences in percentage change in LDL-C from baseline to day 510 were −49.52 (95% confidence interval [CI], −55.04 to −43.99) in ORION-9; −57.64 (95% CI, −60.86 to −54.43) in ORION-10, and −53.5 (95% CI, −56.66 to −50.35) in ORION-11 (all $P < 0.0001$). However, clinically relevant cardiovascular-related morbidity and mortality outcomes were exploratory outcomes, and the trials were not powered to detect statistical significance; hence, the effect of inclisiran on cardiovascular morbidity and mortality has not been determined. Patient input received for this review articulated the need for an additional treatment that would reduce both LDL-C levels and cardiovascular morbidity and mortality. Based on the results from the ORION studies, inclisiran has been shown to reduce LDL-C levels compared with placebo. However, there was insufficient evidence to evaluate the clinical benefit of inclisiran for reducing the risk of cardiovascular events, cardiovascular death, or all-cause mortality in patients with HeFH or nFH with ASCVD.

Given that the effect of inclisiran on cardiovascular morbidity and mortality has not yet been determined, the longer-term safety and efficacy profile of inclisiran requires further evaluation. CDEC noted that there are 2 ongoing studies (ORION-4 and ORION-8) that are expected to 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, as well as provide long-term efficacy and safety data for inclisiran in adult patients with HeFH or nFH with ASCVD, which will contribute valuable information regarding the long-term safety and efficacy of inclisiran.

Direct comparative evidence for inclisiran versus proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (evolocumab and alirocumab) or other add-on agents such as ezetimibe were not identified. 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. There is uncertainty about the ITC results due to the inherent heterogeneity across trials in the networks. Moreover, the sponsor-submitted ITC used study results collected after 24 weeks of treatment, which is a relatively short duration for a chronic condition such as hypercholesterolemia.

Discussion Points

- CDEC discussed that there is no evidence that inclisiran will be better tolerated in patients who did not respond or were intolerant to PSCK9 inhibitors and that the efficacy of switching from PCSK9 inhibitors to inclisiran on reduction in LDL-C levels and cardiovascular morbidity and mortality remains uncertain.
- Given that hypercholesterolemia requires lifelong treatment, CDEC discussed that there is uncertainty regarding the long-term efficacy and safety of inclisiran for the treatment of HeFH or nFH with ASCVD. CDEC also noted that inclisiran has a novel mechanism of action that is different from currently available PCSK9 inhibitors. Currently, this first-in-class mechanism of action has uncertainty around the long-term efficacy and safety. Availability of outcome data from ORION-4 and ORION-8 may help address the longer-term safety and tolerability of inclisiran.

Background

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 either of the following conditions who are on a maximally tolerated dose of a statin with or without other LDL-C–lowering therapies:

- heterozygous familial hypercholesterolemia (HeFH)
- 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.

Sources of Information Used by the Committee

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

- a review of 3 RCTs in adult patients with HeFH or nFH with ASCVD
- patients' perspectives gathered by the patient groups the Canadian Heart Patient Alliance (CHPA) and the HeartLife Foundation
- input from public drug plans that participate in the CADTH review process
- one clinical specialist with expertise in diagnosing and treating patients with HeFH and nFH with ASCVD
- input from an informal clinician group, consisting of lipid specialists and physicians working in lipid clinics in British Columbia, including the Healthy Heart Program Prevention Clinic at St. Paul's Hospital, the Surrey Lipid Clinic at Surrey Memorial Hospital, and the Victoria Lipid Clinic

- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Group Input

Two patient groups, the CHPA and the HeartLife Foundation, provided input for this review. The CHPA is a patient-led, nonprofit umbrella organization of patients, families, health professionals, and supporters dedicated to reducing cardiovascular disease and preventing early death due to cholesterol and other risk factors. Their focus is on high cholesterol and other lipids due to genetic and non-genetic factors because this is the leading under-diagnosed and under-treated cause of cardiovascular disease and early death. The CHPA is the successor to the FH Canada Patient Network and collaborates with FH Canada, the Heart Healthy Prevention Program St. Paul's Hospital, and the Lipid Genetics Clinic at London Health Sciences Centre–University Hospital. The HeartLife Foundation is a patient-driven charity whose mission is to transform the quality of life for people living with heart failure by engaging, educating, and empowering a global community to create lasting solutions and build healthier lives.

The information provided by CHPA was gathered from a total of 262 individuals through an online survey (n = 254) and individual interviews (n = 8). The information provided by the HeartLife Foundation was gathered through discussions held with 8 to 12 individual members across Canada. Members included both patients living with heart failure and their family caregivers. The discussions were held as informal online group conversations or via a phone call with individuals.

Approximately 25% of respondents to the CHPA survey reported regular physical symptoms related to their lipid levels, some minor and some significant, including headaches (like "icy picks"), chest pains, muscle pains in legs and ankles, shortness of breath, xanthomas (under the skin in wrists, ankles, or elsewhere), weakness, fatigue, muscle loss, and neuropathy. Approximately 20% also indicated that managing their cholesterol level and keeping it at target was an ongoing challenge, while another 20% said that their high cholesterol and/or lipid condition had little or no effect on their quality of life. Many reported that they had changed their diet and exercise. However, some responses indicated that patients were not always aware of the impact of high cholesterol in part because they were well-managed on treatment and did not experience daily symptoms. Most respondents felt positive about their daily life and had accepted or adapted to living with high cholesterol, including those who experienced a cardiovascular event or had stents. The 2 most frequently mentioned sources of anxiety were future uncertainty of the medications not working or the risk of a cardiovascular event and the impact on their children, whether diagnosed or at risk.

The majority of respondents to the survey by the CHPA expressed multiple concerns, largely about treatment schedules, side effects, and cost of current therapies. For respondents, the most important impact was knowing that there was a treatment that could lower their cholesterol levels and keep them closer to target, thereby reducing the risk of further cardiovascular events. Public reimbursement for PCSK9 inhibitors in Canada is limited, and access for patients with uncontrolled LDL-C is highly restricted by provincial health benefit program reimbursement criteria.

Clinician Input

The clinical expert consulted by CADTH for this review indicated that many patients are unable to meet the pre-specified LDL-C thresholds outlined in the *Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult* and *Canadian Cardiovascular Society Position Statement on Familial Hypercholesterolemia* for current treatments, and there is an unmet need for additional treatment options that further reduce LDL-C levels. Statins are considered the standard treatment for the prevention of ASCVD in high-risk patients and in patients with FH or severe hypercholesterolemia; however, the clinical expert pointed out that up to 15% of patients are partially or completely intolerant to statins.

It was also emphasized by the clinical expert that the Canadian Cardiovascular Society guidelines should be used as a basis for recommendation in identifying and treating patients (in patients with HeFH without clinical ASCVD whose LDL-C remains above the target LDL-C ≥ 2.5 mmol/L or < 50% reduction from baseline despite maximally tolerated dose [MTD] statin therapy with or without ezetimibe therapy, or patients with HeFH and ASCVD whose LDL-C remains ≥ 1.8 mmol/L despite MTD statin therapy, with or without ezetimibe), and that appropriate patients should match the characteristics of the patients enrolled in the clinical trials included in this review. The clinical expert suggested that patients considered most likely to exhibit a response to treatment with inclisiran, according to the clinical expert, were those who achieved a 30% to 40% reduction in LDL-C from baseline levels (while on optimized statin ± ezetimibe therapy) and require further lowering of LDL-C. Patients least suitable for treatment with the drug under review were those with low-risk ASCVD, low-risk severe hypercholesterolemia well-controlled with statins, ASCVD patients at LDL-C goals with current therapies, primary prevention in patients with nFH who are older than a certain age, and patients with multiple comorbidities that limit lifespan.

The clinical expert stated that percent reduction in LDL-C and absolute level of LDL-C achieved are outcomes used in clinical practice to determine response to treatment. The clinical expert indicated that treatment response should be assessed every 6 months, then yearly. The clinical expert stated that age, end-stage disease, and/or dementia are important factors that should be considered when deciding to discontinue treatment.

Clinician Group Input

A group of clinicians consisting of lipid specialists working in lipid clinics in British Columbia, including the Healthy Heart Program Prevention clinic at St. Paul's Hospital, the Surrey Lipid Clinic at Surrey Memorial Hospital, and the Victoria Lipid Clinic provided input for this review.

The clinician group noted the tolerability of current treatments, compliance, ability to treat to target lipid levels, and accessibility as the current unmet needs in treating patients with HeFH and/or ASCVD. The clinician group described an ideal treatment option as one that would reduce levels of LDL-C, non-high-density lipoprotein cholesterol (non-HDL-C), and apolipoprotein B (ApoB); reduce the risk of major adverse cardiovascular events and cardiovascular mortality; and be safe and well-tolerated, with properties that promote adherence.

The clinician group noted that patients with the greatest unmet need for intervention are those with HeFH, patients with statin intolerance, and patients with ASCVD with other markers of high risk, such as multivessel disease, polyvascular disease, diabetes, and elevated lipoprotein(a). They also noted that the patients least suitable for treatment with the

drug under review would be patients who do not have an indication for the therapy, who have achieved LDL targets on other therapies (statin with or without ezetimibe), or who have not attempted a statin.

The clinician group noted that inclisiran may displace currently available PCSK9 inhibitors (evolocumab and alirocumab) as an add-on to statins and ezetimibe if it is more accessible than current treatments and depending on the results of currently ongoing cardiovascular outcome trials. It may also fill a void if it is approved for high-risk secondary prevention patients.

Drug Program Input

Input was obtained from the jurisdictions participating in CADTH reimbursement reviews. The following were identified as key factors that could impact the implementation:

- Patient population definitions and variability in treatment according to Canadian guidelines.
    - The clinical expert consulted by CADTH for this review indicated that, overall, initiation criteria for inclisiran may follow that of currently available PCSK9 inhibitors (evolocumab and alirocumab), with patients first receiving MTD statins, followed by ezetimibe if within 20% of LDL-C target, or PCSK9 inhibitors if greater than 20%. The cut point targets of 2.6 mmol/L (> 2.5 mmol/L) for HeFH and 1.8 mmol/L for patients with ASCVD are reflective of the guidelines for these populations.
- Whether laboratory assessments were appropriate outcomes for assessing effectiveness in the real world.
    - The clinical expert noted that LDL-C, ApoB, and non–HDL-C are guidelines recommended biomarkers for cardiovascular outcomes. It was also noted that inclisiran may follow the same initiation and renewal criteria as currently available PCSK9 inhibitors, and that the occurrence of cardiac events would not warrant discontinuation.
- Whether inclisiran would be used in patients who do not have hypercholesterolemia or who have had a prior myocardial infarction or stroke (i.e., for primary prevention).
    - The clinical expert noted that elevated LDL-C can be caused by other diseases; these should be addressed separately and are therefore not within the context of this review.

Clinical Evidence

Clinical Trials

Description of Studies

A total of 3 studies were included in this review: ORION-9, ORION-10, and ORION-11. The included studies were all phase III, double-blind RCTs comparing inclisiran with placebo in patients with HeFH or ASCVD (and ASCVD risk equivalent [i.e., those with diabetes, FH, or a 10-year risk of a cardiovascular 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 trial were adults (≥ 18 years) with 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 greater than 190 mg/dL, and a family history

of FH, elevated cholesterol or early heart disease that may indicate FH. Patients enrolled in the ORION-10 trial were adults (≥ 18 years) with a history of ASCVD; patients enrolled in the ORION-11 trial were adults (≥ 18 years) with a history of ASCVD or were ASCVD risk equivalent. In all 3 ORION studies, patients were randomized 1:1 to either inclisiran sodium 300 mg or placebo in addition to MTD statin. The ORION-9, ORION–10, and ORION–11 trials enrolled 482, 1,561, and 1,617 patients, respectively. The studies were all 18 months in duration with patients receiving one 300 mg dose of inclisiran sodium on day 1, day 90, day 270, and day 450, for a total of 4 doses. The primary outcome of the ORION-9, ORION–10, and ORION–11 trials was the percentage change in LDL-C from baseline to day 510. In all trials, the co-primary end point was the average percentage change in LDL-C from baseline for the period from day 90 up to day 540, reflecting the start of the biannual dosing regimen. Incidences of cardiovascular death, resuscitated cardiac arrest, non-fatal myocardial infarction, and non-fatal stroke (ischemic and hemorrhagic) were exploratory outcomes in the ORION trials within the composite outcome of major cardiovascular events (MACE); total deaths was a secondary outcome reported as adverse events (AEs) in the ORION studies.

Baseline characteristics were well-balanced across groups in each trial. In the ORION-9 trial, patients were primarily White (94.0%), with a median age of 56 years, and more than half of the patients were female (52.9%). Cardiovascular risk factors were balanced between the treatment groups. Overall, 350 (72.6%) patients were ASCVD risk equivalent and 132 (27.4%) had ASCVD. A total of 356 (73.9%) patients were treated with high-intensity statins at baseline, and just over half were treated with ezetimibe. Partial or complete intolerance to statins was reported in 122 (25.3%) patients. In the ORION-10 trial, patients were primarily White (85.7%), male (69.4%), with a median age of 67 years. All patients had ASCVD, and most had CHD (91.1%). A total of 1,084 (69.4%) patients were on high-intensity statins at baseline, and 156 (9.9%) patients were treated with ezetimibe. Partial or complete intolerance to statins was reported in 344 (22.0%) of patients.

In the ORION-11 trial, patients were primarily White (98.1%), male (71.7%), with a median age of 65 years. Cardiovascular risk factors were balanced between the treatment groups; 1,414 (87.4%) had ASCVD and 203 (12.6%) were ASCVD risk equivalent. The non-HeFH ASCVD risk equivalent population from the ORION-11 trial were not of interest to this review because they were not included in the funding request. Overall, 1,261 (78.0%) patients were on a high-intensity statin at baseline. A total of 114 (7.1%) patients were treated with ezetimibe. Partial or complete intolerance to statins was reported in 185 (11.4%) patients.

Efficacy Results

All-cause and cardiovascular-related mortality were assessed as AEs in the ORION-9, ORION–10, and ORION–11 trials, and were reported as the incidence of death within the safety population. In the ORION-9 trial, only 2 deaths occurred (0.4%): 1 in each treatment group. A total of 23 patients died during the ORION-10 study: 12 (1.5%) in the inclisiran group and 11 (1.4%) in the placebo group. In total, 29 (1.8%) patients died during the ORION-11 study, 14 (1.7%) in the inclisiran group and 15 (1.9%) in the placebo group. Deaths were related most frequently to cardiac disorders as a system organ class, ranging from 1 (0.4%) patient to 7 (0.9%) patients in the ORION-9, ORION-10, and ORION–11 trials.

Although not referred to as cardiovascular-related morbidity in the ORION trials, for the purposes of this review, the incidence of MACE and its composite components were considered as cardiovascular-related morbidity and it was an exploratory outcome of the ORION trials. No between-group comparisons were conducted in the ORION-9, ORION–10,

and ORION−11 trials for this outcome. The incidence of MACE in the inclisiran groups was consistently similar to or lower than placebo groups across all trials (4.1% versus 4.2%, 7.4% versus 10.2%, and 7.8% versus 10.3%, in ORION-9, ORION−10, ORION−11, respectively). Non-fatal MI was the most frequently occurring individual event across all trials, occurring in 3.7% versus 4.2%, 5.1% versus 8.2%, and 5.8% versus 8.5% of patients in the inclisiran and placebo groups of the ORION-9, ORION−10, and ORION−11 trials, respectively. No resuscitated cardiac arrest or stroke events occurred in the ORION-9 trial. Other cardiovascular-related morbidities of interest to this review, including hospitalizations and minimally invasive cardiovascular interventions, were not reported in the ORION trials.

The primary efficacy end point of the ORION-9, ORION−10, and ORION−11 trials was the percentage change in LDL-C from baseline to day 510. In all ORION trials, inclisiran reduced LDL-C levels from baseline to day 510 (ORION-9: −41.15% [95% CI, −44.52 to −37.77]; ORION-10: −56.34% [95% CI, −58.35 to −54.34]; and ORION-11: −49.3% [95% CI, −51.22 to −47.48]), while the change from baseline LDL-C levels increased with placebo (ORION-9: 8.37% [95% CI, 3.96 to 12.77]; ORION-10: 1.30% [95% CI, −1.24 to 3.83]; and ORION-11: 4.2% [95% CI, 1.62 to 6.69]). Between-group differences were statistically significant in favour of inclisiran in all studies with differences from placebo of −49.52 (95% CI, −55.04 to −43.99) in ORION-9, −57.64 (95% CI, −60.86 to −54.43) in ORION-10, and −53.5 (95% CI, −56.66 to −50.35) in ORION-11 (all P < 0.0001). The clinical expert consulted by CADTH considered the between-group differences in LDL-C levels to be clinically meaningful.

Results for key secondary outcomes in the ORION trials of absolute change in LDL-C from baseline to day 510, time-adjusted change in LDL-C from baseline for the period after day 90 up to day 540, and percent change from baseline to day 510 in total cholesterol, ApoB, and non-HDL-C were consistent with the co-primary end points. For absolute change in LDL-C from baseline to day 510, inclisiran displayed larger absolute reduction in LDL-C (ORION-9: −58.95 [95% CI, −64.75 to −53.15] mg/dL; ORION-10: −56.18 [95% CI, −58.47 to −53.90] mg/dL; ORION-11: −50.91 [95% CI, −53.14 to −48.67] mg/dL), and between-group differences were statistically significant in favour of inclisiran in all studies (ORION-9: −68.89 [95% CI, −77.11, −60.67] mg/dL; ORION-10: −54.12 [95% CI, −57.37, −50.88] mg/dL; ORION-11: −51.87 [95% CI, −55.01, −48.72] mg/dL; all P < 0.0001). In all trials, inclisiran was associated with greater absolute reductions in LDL-C from baseline for the period after day 90 up to day 540 (ORION-9: −56.58 [95% CI, −60.98, −52.17] mg/dL versus 6.17 [95% CI, 1.72, 10.62] mg/dL; ORION-10: −53.66 [95% CI, −55.41 to −51.92] mg/dL versus −0.39 [95% CI, −2.14 to 1.37] mg/dL; and ORION-11: −48.63 [95% CI, −50.37 to −46.89] mg/dL versus [95% CI, −1.42 to 2.04] 0.31 mg/dL), and the mean difference between inclisiran and placebo was statistically significant in all trials (P < 0.0001). Lastly, results for percentage change in TC, ApoB, and non-HDL showed greater percentage changes for the inclisiran groups in all studies; the mean difference from placebo was statistically significant in all cases (P < 0.0001).

Other outcomes of interest to this review, including HRQoL and neurocognitive assessments, were not included in the ORION trials.

Harms Results

The incidence of treatment-emergent AEs was consistent between inclisiran and placebo-treated patients as well as across trials, with patients experiencing at least 1 treatment-emergent AE in 76.8% versus 71.7%, 73.5% versus 74.8%, and 82.7% versus 81.5% in the ORION-9, ORION−10, and ORION−11 trials, respectively. There was no difference in the frequency of treatment-emergent serious AEs between the treatment groups in the ORION-9,

ORION-10, and ORION-11 trials. Treatment-emergent serious AEs in the ORION-9 trial occurred in 7.5% of inclisiran-treated patients and 13.8% of placebo-treated patients. In the ORION-10 and ORION–11 trials, serious AEs occurred in 22.4% and 22.3% of inclisiran-treated patients compared with 26.3% and 22.5% of placebo-treated patients. In the ORION-9 trial, 1.2% of patients in the inclisiran group withdrew due to an AE, whereas no patients in the placebo group withdrew due to AEs. The incidence of withdrawals due to AEs in the ORION-10 and ORION-11 trials were similar, with 2.4% and 2.8% of inclisiran-treated patients and 2.2% of placebo-treated patients withdrawing due to AEs in each trial, respectively.

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

Indirect Comparisons

The sponsor submitted an ITC that compared the efficacy of inclisiran to relevant drug comparators in patients with HeFH or ASCVD (or ASCVD risk equivalent). The objective of the sponsor-submitted report was to conduct a feasibility assessment via a 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 currently available PCSK9 inhibitors (evolocumab and alirocumab) in patients with HeFH or ASCVD (or ASCVD risk equivalent).

The sponsor-submitted ITC was informed by a systematic review of RCTs that was conducted in April 2020. Thirty-nine studies met the inclusion criteria of the review and feasibility assessment, and 22 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; percent change from baseline in HDL-C; safety outcomes included total discontinuations; and discontinuations due to AEs.

Efficacy Results

A total of 7 trials were included in the network for the HeFH population on MTD statins; 13 studies were included in the base case network for the ASCVD and risk equivalent populations on MTD statins, in which 1 closed loop was formed; and 7 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 regarding background statin use and the time of assessment of outcomes, which impacted clinical and methodological heterogeneity and resulted in limited interpretability and generalizability of the results. Although 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, 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 because of 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 with the dosing regimen of every 2 weeks for 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 because 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.

Other Relevant Evidence

Two additional relevant studies (ORION-4 and ORION-8) were noted in the sponsor submission and identified in the CADTH screening of clinical trial databases. At the time of this review, results were not available for either of these studies. As such, the ORION-4 and ORION-8 trials were not included in the previous discussion of available evidence. The ORION-4 trial aims to evaluate the efficacy of inclisiran in lowering the risk of MACE of congenital heart disease, myocardial infarction, fatal or non-fatal ischemic stroke, or urgent coronary revascularization procedure, or the composite of congenital heart disease death or myocardial infarction, and the risk of cardiovascular death in patients with ASCVD. ORION-8 is an extension study of the ORION-5, ORION–9, ORION–10, and ORION–11 trials to evaluate the long-term efficacy, safety, and tolerability of inclisiran in patients with ASCVD, ASCVD risk equivalent, HeFH, or HoFH, who still had elevated LDL-C despite maximum-tolerated

LDL-C–lowering therapies through measures of LDL-C. Results of these trials are expected to provide further evidence to better characterize the efficacy profile of inclisiran in pertinent clinical outcomes, as well as provide long-term efficacy and safety data for inclisiran.

Economic Evidence

Table 1: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target populations	Adult patients with HeFH or clinical ASCVD who require additional lowering of LDL-C despite maximally tolerated statin therapy
Treatments	Inclisiran + SoC (defined as maximally tolerated statins with or without ezetimibe)
Submitted price	Inclisiran, 284 mg: $2,839.28 per pre-filled syringe
Treatment cost	Initial year: $8,518 Subsequent years: $5,679
Comparator	ASCVD patients: SoC HeFH patients: SoC, evolocumab + SoC; alirocumab + SoC
Perspective	Canadian publicly funded health care payer
Outcome	QALYs, life-years
Time horizon	Lifetime (40 years)
Key data source	The impact of treatment on LDL-C was informed by network meta-analyses for inclisiran (ORION-9, ORION-10, ORION-11), evolocumab, and alirocumab. SoC was assumed to have no effect on LDL-C level.
Key limitations	• The effect of inclisiran on cardiovascular outcomes is highly uncertain. The predicted survival benefit for patients treated with inclisiran has not been shown in clinical trials. The sponsor's model used a surrogate outcome, LDL-C, to approximate the relationship between treatment and cardiovascular risk. • The comparative clinical effectiveness of inclisiran vs. PCSK9 inhibitors is highly uncertain. There have been no head-to-head trials of inclisiran vs. PCSK9 inhibitors, and there is substantial uncertainty in the results of the sponsor's network meta-analyses. • The sponsor considers relative, but not absolute, changes in LDL-C levels. The clinical expert consulted by CADTH for this review indicated that absolute changes may be a more relevant measure of effect for patients with HeFH. • The baseline risk of cardiovascular events in the modelled population may not reflect risk in the Canadian population. • Inclisiran was assumed to maintain consistent treatment effectiveness over the model's 40-year analysis horizon. The long-term effectiveness of inclisiran has not been assessed beyond 18 months of treatment in clinical trials. • The sponsor employed poor modelling practices in their model, preventing CADTH from fully validating the model and its findings.

Component	Description
CADTH reanalysis results	• In CADTH reanalyses, in light of the high level of uncertainty in the comparative clinical evidence, the effectiveness inputs are informed by direct evidence from the ORION-9 (HeFH subgroup) and ORION-10 (ASCVD subgroup) trials, with pairwise comparison of inclisiran plus SoC vs. SoC alone. In addition, a similar relationship was assumed between LDL-C reduction and cardiovascular risk as observed with evolocumab in the FOURIER trial. CADTH was unable to address the inability to reflect the effect of inclisiran on absolute changes in LDL-C in the HeFH subgroup, uncertainty regarding the baseline risk of cardiovascular events, and uncertainty regarding long-term clinical effectiveness of inclisiran. • Based on CADTH reanalyses, inclisiran plus SoC remained more costly and more effective than SoC alone in both the ASCVD and HeFH subgroups: ◦ ASCVD subgroup: ICER = $366,650 per QALY (incremental costs = $58,286; incremental QALYs = 0.16). ◦ HeFH subgroup: ICER = $626,458 per QALY (incremental costs = $95,065; incremental QALYs = 0.15). • A price reduction of 83% would be required for inclisiran to be considered optimal at a WTP threshold of $50,000 per QALY in the ASCVD subgroup, while a price reduction of 91% would be required for inclisiran to be considered optimal in the HeFH subgroup.

ASCVD = atherosclerotic cardiovascular disease; HeFH = heterozygous familial hypercholesterolemia; ICER = incremental cost-effectiveness ratio; LDL-C = low-density lipoprotein cholesterol; QALY = quality-adjusted life-year; SoC = standard of care; vs. = versus; WTP = willingness to pay.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the number of patients eligible for public drug coverage of inclisiran was underestimated and the market uptake of inclisiran is uncertain. CADTH reanalysis included changing the percentage of patients eligible for public drug plan coverage, changing the proportion of HeFH patients diagnosed, and aligning the cost of statin therapy with the pharmacoeconomic submission.

Based on the CADTH reanalyses, the budget impact from the introduction of inclisiran for the reimbursement request is expected to be $368,202,533 in year 1, $720,442,871 in year 2, and $878,899,801 in year 3, with a 3-year total budget impact of $1,967,545,205. The 3-year budget impact of reimbursing inclisiran for the ASCVD subgroup was estimated to be $1,962,723,725 and $4,821,480 for the HeFH subgroup. The estimated budget impact is sensitive to the prevalence of ASCVD and the market uptake of inclisiran.

CDEC Information

Initial Meeting Date: August 18, 2021

Members of the Committee

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Dr. Kerry Mansell, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets: Two CDEC members did not attend

Conflicts of interest: None

Reconsideration Meeting Date: January 26, 2022

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Regrets: One CDEC member did not attend

Conflicts of interest: None