CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

inclisiran (Leqvio)

(Novartis Pharmaceuticals Canada Inc.)

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.

July 14, 2023

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

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Patient Input

Patient Input

Name of Drug: Inclisiran (Leqvio)

Indication: Atherosclerotic Cardiovascular Disease (ASCVD)

Name of Patient Group: Canadian Heart Patient Alliance (CHPA)

Author of Submission: Durhane Wong-Rieger

1. About Your Patient Group

The Canadian Heart Patient Alliance (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 genetic, environmental, lifestyle, and other risk factors. Our focus is improving awareness, screening, testing, diagnosis, care, and treatment of all CVDs. The Canadian Heart Patient Alliance is working toward the day when no Canadian will suffer reduced quality of life, life-altering event, or early death due to undiagnosed or untreated CVD.

The Canadian Heart Patient Alliance collaborates with FH Canada, Heart Healthy Prevention Program St. Paul's Hospital, and Lipid Genetics Clinic at LHSC-University Hospital. Internationally, CHPA engages with the FH Foundation (USA), Heart UK, and FH Europe.

Website: http://www.heartpatientalliance.ca/

2. Information Gathering

While atherosclerosis is a leading cause of morbidity and mortality, most people affected do not recognize it as a serious condition. Similarly, patients at high risk for atherosclerotic cardiovascular disease (ASCVD**)** often do not take action until they have experienced a catastrophic event, like stroke, heart attack, or peripheral nerve damage. Awareness, education, screening and diagnosis for inherited hypercholesterolemia, and improved lipid-regulation medication have significantly reduced the risk of ASCVD. However, there are patients who are intolerant to or whose cholesterol is not significantly controlled by current medications, notably statins, ezetimibe, and PCSK9.

Our goal in this submission was to provide feedback from Canadian patients with ASCVD who had experience with inclisiran (Leqvio), as well as other patients who have suffered serious cardiac events, are diagnosed with ASCVD, or at high risk for ASCVD due to insufficiently controlled cholesterol levels.

A survey questionnaire was developed and made available through Survey Monkey from 8 June to 10 July, 2023.

Our initial step in recruitment was outreach through the CHPA mailing list and St. Paul's Hospital Healthy Heart Program FH patient list, targeting patients with or at high risk for ASCVD (definition provided in outreach email). At the end of the survey, we asked participants whether they would be willing to participate in an individual interview and, if so, to provide an email address and/or phone number. In addition, we directly contacted cardiologists who were identified as having prescribed inclisiran to patients with ASCVD through clinical trials or other access pathways. We asked them to (1) pass on the survey link to appropriate patients and (2) request patients who have received inclisiran to take part in an individual interview.

We received 85 survey responses. Of these, 58% of identified as having a diagnosis of ASCVD (39%) or had experienced a heart attack or stroke (19%). Another 27% responded that they had symptoms of or were at "high risk" for ASCVD. Overall, 67% reported they were also diagnosed with familial hypercholesterolemia and 25% had other lipid disorders (dyslipidemia, hyperlipidemia, high triglycerides).

In terms of age, the most frequent age category was "60 to 69 years of age" (31%), followed by age category "over 70 years" (23%), with 12% reporting (50 to 59 year of age", and another 9% "40 to 49 years of age". Only 6% reported they were 30 to 39 years of age" and 2% between "20 to 29 years of age."

In addition, we conducted interviews with 10 individuals, four referred by their physicians and six who volunteered through the survey. All had diagnosis of ASCVD or had experienced a heart attack or stroke and had received inclisiran.

Among the 10 interviewed patients, six identified as male and four as female. They ranged in age from 46 years old to 83 years old. All resided in Canada, with the majority (four respondents) in Ontario, four in B.C., and two in Alberta.

3. Disease Experience

Participants were asked, in an open-ended question, to … "Describe, in your own words, how living with high cholesterol or high lipids or cardiovascular disease has affected you currently or in the past. Has your condition affected your work, school, social and/or family life?

The following responses come from the subset of those surveyed who identified as diagnosed with ASCVD, experienced a heart attack or stroke, or have symptoms which put them at high risk for ASCVD. However, to put their responses in context, it is important to know that 90% are being managed in a cardiovascular program and all reported receiving regular follow up care by a specialist or their family physician.

The open-ended responses of respondents living with ASCVD and ASCVD risk showed that all experienced significant impact in six key areas; cholesterol management, lifestyle impact, cardiovascular events, treatments, stress/anxiety, and family impact. The following are some of the verbatim responses. All describe ASCVD as having had a significant impact on their quality of life. Many described the impact of a heart attack, bypass surgery or stroke on themselves and their families, especially in some cases where they have active lifestyles, busy, careers, and young 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 and, in turn, the impact of the condition on their children. All the respondents in this group had experience with statins and other medications, with varying degrees of success.

The following are some of the verbatim descriptions of their experience living with ASCVD.

"My father died at 53 after having his 4th heart attack in 3 years. His brother who was 10 years younger had a quadruple bypass at 50 years old. I have familial high cholesterol and am not able to have it under control no matter what I do."

"My life with cardiovascular health issues have been extremely stressful and difficult, I have been on medications for ninety percent of my life with little help. I had two open heart surgeries with a lot of stress for me and my family. Unfortunately, the cost of the recent medications I cannot afford"

"Many on my Father's side of the Family passed with heart disease. I am presently very calcified, so a 2nd TAVI surgery for my aortic valve can't be done. A combined aortic and mitral valve replacement is very risky. I was one of the first to have the TAVI, and it has now been almost 15 years since that time. I realize I may not have much longer to live, but am doing fine right now. Today, my doctor today again mentioned my very audible heart murmur. I had to give up some of my sports, the past 3 years, but am still cycling, walking and swimming."

"I was diagnosed with CAD and hypertension with familial high cholesterol in 2010. I was working full time as. RN at the time. My coronary status stabilized quickly and I returned to work. I became very fatigued with muscle pain, after extensive investigations it was determined that my body reacts to all statins. My muscles wasted. I was forced to retire from work. I was eventually trialled on Repatha, which helped immensely. Overtime I've had to reduce my dose of Repatha due to muscle pain and fatigue. My blood work remains in the normal range but is not optimal for my known CA D. It might benefit me to try this new medication but it's not available to me at this time."

"Living with cardiovascular disease has severely affected the quality of my life. I have been on a myriad of trials of cholesterol lowering statins, all of which I could not tolerate, as they caused severe muscle spasms, which made my life intolerable. Many of these required at least a six-month trial to see if they were effective, and if the symptoms would abate. Even tying very reduced dosages of these statins, would cause my leg muscles to spasm affecting my mood and quality of life (mobility and sleep)."

"I experienced stable angina three years ago, and was soon diagnosed with an 80% blockage of a coronary artery and treated with a stent. It was a scary time. I am now on medications to reduce my cholesterol, which is reassuring but this is still scary."

"I was diagnosed with high cholesterol in my late 20's to early 30's. I have been on a lipid lowering medication from my mid 30's My diet has always been a concern, and I've had advice to eat veggies and keep fit. I was also advised to eat Becel margarine which I abhorred. I found jogging/running a great outlet until my early 50's when i was diagnosed with severe hip issues, I then had my first hip surgery at age 55 and second at age 59. I miss being able to jog/run greatly and my weight is increasing as I age."

"I have familial high cholesterol, so I have taken statins for 40 years with varying side effects and dieted a lot. The drugs are expensive, and they have pushed my blood sugar dangerously high. I also have muscle pain that may be a side effect."

"Many on my Father's side of the Family passed with heart disease. I am presently very calcified, so a 2nd TAVI surgery for my aortic valve can't be done. A combined aortic and mitral valve repalcement is very risky. I was one of the first to have the TAVI, and it has

now been almost 15 years since that time. I realize I may not have much longer to live, but am doing fine right now. Today ,my doctor today again mentioned my very audible heart murmur. I had to give up some of my sports, the past 3 years, but am still cycling, walking and swimming."

"I was put on high doses of statins together with Ezetrol which worked to bring my levels down somewhat but not enough according to target levels considered optimal for lowering risk of another MI. When Repatha became an option- I was put on this medication and continued eating a healthy diet and exercising regularly. It took me a long time to be able to give myself the injection bi-weekly, but I persisted and finally was able to do this. I had a lot of damage from the initial heart attack so I've been living with congestive heart failure all these years (I'm now 73)- I've been on many medications for dealing with arrhythmias and cardiac function. Recently I've needed to have an implant to help with pacing which also has a defibrillator within it. I'm followed closely by the pacemaker clinic and cardiologist for managing heart function and the CHF."

"At the age of 36 I experienced an MI one evening while sitting with my 2 children who were aged 7 and 9 at the time. I was a single parent of 2 children and had recently completed 4 years of university, obtaining a Bachelor of Social work degree. I thought I was in good health as I was health conscious and of normal weight, exercised regularly and lived a moderate lifestyle with a focus of parenting my kids to the best of my abilities. I had a student loan to pay off and had recently been hired at a hospital- I had only been working in my job for about 6 weeks so didn't have many sick days built up and didn't qualify for sick benefits from my job- I was told I'd need at least 3 months off work to recover - my only option was to apply for income assistance which wasn't enough to cover my rent, so my sister offered to let the 3 of us move into her basement until I was able to return to work. … Initially I wasn't out on anything to lower my cholesterol levels but I tried my best to remove food items such as cream, cheese, butter, eggs - things that were known to affect cholesterol levels- however my levels remained high. Over the years I was out on various medications to lower levels - some had a little effect, others helped more but had side effects which were difficult to deal with."

"I'd say my life since the heart attack in 1987 has been dominated by managing my health and trying to moderate my lifestyle to live my healthiest life. Having had the heart attack also affected my ability to qualify for mortgage insurance, life insurance, travel insurance- I've had to try to advocate for myself to try to get meds I've been prescribed covered under health plans - often over the years I had to pay out of pocket for medication that was not covered provincially and therefore not covered by my blue cross plan from work. At one point I had maxed out my blue cross plan limit and had to pay for all my meds out of pocket."

4. Experiences With Currently Available Treatments

TREATMENTS: Respondents' perceptions of their treatments were drawn from the open-ended experiential question as well as two rating scales about seven (7) treatments: low-fat diet, statin (such as, atorvastatin (Lipitor), rosuvastatin (Crestor), simvastatin (Zocor)), ezetimibe (Ezetrol, Zetia or Vyotorin), apheresis (to remove LDL-C from bloodstream), lomitapide (Juxtapid) or Mipomersen (Kynamro), evolocumab PCSK9 inhibitor (Repatha), alirocumab PCSK9 inhibitor (Praluent), inclisiran PCSK9 inhibitor (Leqvio), and other. They were asked to rate, first, on the effectiveness of each therapy, that is, "how well this therapy has worked to keep cholesterol at the desired level" (three-option scale) and the experience of adverse effects, namely, "the degree to which you experienced side effects related to the treatment" (three-option scale).

EFFECTIVENESS: Overall, 100% said they had used a low-fat diet but 56% said this was not all effective. Only 10% felt this was effective.

Almost all (92%) had been prescribed statins, and while 44% said these were effective or very effective, 37% said they were only somewhat effective while 11% said "not at all or very little."

The vast majority (87%) had also been prescribed ezetimibe, but these were rated as not much more effective than statins (40% effective or very effective and 16% not at all or very little).

More than half (57%) had been prescribed PCSK9 (Repatha or Praluent) and, of these, most (92%) said they were effective or very effective. Only 6% reported they did not work.

Importantly, 14% (6 survey respondents) had experience with inclisiran. Among these, 83% (5) said it was effective or very effective and 17% (1) said it was not effective in lowering cholesterol to target levels.

SIDE EFFECTS: In terms of side effects, the ratings were somewhat the obverse of effectiveness. In terms of statis, about one third (38%) said they had experienced little or no side effects and another 38% said they experienced moderate adverse effects, while 26% said the side effects were severe. In previous survey, respondents reported:

"I also was not able to tolerate any form of statin, many were tired to little effect of sufficiently lowering my numbers nor could I tolerate the side effects of the statin. Being on Repatha, has been very efficient for me.

"I have high cholesterol but cannot take more than 10 mg vastatin since it gives me muscle pain. Vastatin also has other side effects such as dry mouth and I feel it is hard to treat and Biotin mouth wash does not help much. I am very careful with my diet and try to exercise as much as I can."

"While taking a specific statin drug, I experienced severe pain in my muscle tissue in various parts of my body. Laboratory results confirmed that my creatine kinase (CK) levels were dangerously high. The muscle pain from the statin was severe and caused me to have difficulty walking."

The report of side effects to ezetimibe were considerably less than to statins, with 68% of those who had received the therapy experienced little or no side effects, 21% reporting some or moderate side effects, and only 9% experiencing serious side effects.

Similarly, side effects to PCKS9s were very low. Overall, among those who had received one of the two PCSK9s, 86% said they had experienced few or no side effects, while 14% said there were some or moderate side effects. None reported any serious side effects. These comments come from our previous respondents,

"I was one of the very early patients introduced to the injectable PCSK9 inhibitors … to be used in combination with statins. My cholesterol levels did retreat … but I again had an adverse reaction to the statin which resulted in muscle pain and a significantly high CK level. My body is able to tolerate the PCSK9 inhibiter but alone, it has not been successful."

"At present, no drug alone or in combination has been successful in managing my cholesterol level and statins have caused severe side effects. The PCSK9 inhibiter, while tolerable without adverse side effects, has shown a small measurable decrease in cholesterol levels but not significant enough to be called successful."

"Managed with statins for a while, but muscle cramping precluded that option. Repatha seems to work well."

"My body does not tolerate the many statins I have used and causes significant elevations to my CK and liver levels. Hence, I have been taking PCSK9 along with low doses of Crestor, along with Ezetimibe to aggressively manage the LDL levels. These drug use over the years have caused many side effects such as muscle and joint pain, low libido, sleep problems, and headaches over the years. They have led to anxiety and depression. The physical symptoms have made it difficult to engage in regular sports, exercise and personal and intimate relationships in order to enjoy a high-quality life."

Finally, all of those on inclisiran reported none or very few side effects.

In summary, most of these respondents who had ASCVD or were at high risk for ASCVD reported their cholesterol levels were not well managed on diet alone. Almost all had used statins, with about 44% reporting they worked well alone or in combination with another drug. More than half (57%) had been prescribed PCSK9, with about 92% of those on the drug reporting they worked well or very well to manage their cholesterol levels. Finally, almost all who had been prescribed inclisiran found them to be effective with no or little side effects.

5. Improved Outcomes

Patients were asked about their expectations for inclisiran, based on what they knew, or their general expectations for improved therapy.

Overall, respondents expressed fairly straightforward desires and expectations for inclisiran or other improved therapies. First and foremost, they wanted a therapy that was effective in lowering and keeping cholesterol to levels where they could live a "long and normal life." Second, most wanted improved safety, that is, fewer and more tolerable side effects. A third desire was for a more manageable treatment regimen or protocol, including less frequent dosing, easier administration, and less disruptive to work or daily life. Finally, patients wanted treatments to affordable.

Said one person, “My expectations is that it will reduce my levels of cholesterol to prevent further heart disease and blood circulation problems. By doing so I hope to experience a longer life than my farther who died at the age of 38.”

Similarly, another patient said, *“I would hope t could remove the built-up calcification. Nothing else is solving that problem for me.”*

“… with Repatha it’s biweekly so if someone wanted to travel for longer than 2 weeks it wouldn’t be such an issue as it is for Repatha, which has to be refrigerated.”

“I hope that it provides long lasting cholesterol control, which will ultimately be lifesaving and cost saving for our healthcare system.”

“Compliance can be a major hurdle.”

Some who had familial high cholesterol also expressed desire that there would be more effective, safer, and easier therapies for their

6. Experience With Drug Under Review

All of the 10 patients who had received inclisiran got it through clinical trials or access program. Most had received only one or two injections, although one patient believed he had received four doses.

Among this cohort, nine reported that it was highly effective although do not have experience about long-term outcomes.

“I do use it and am getting good results. Hope it will help others.”

“Leqvio dramatically reduced my LDL levels within the first six months. My expectation is that it will continue to do so, and I would expect that it would have similar success in others.”

“I have only just started on it so do not yet have an idea of what my response to it will be [over time].”

“… this drug needs to only be used a couple times a year and it brings cholesterol levels way down. My hope for this drug is that it [will] reduce cardiac events and allow [me] to live happier more fulfilled live … and [my family] can feel safe from heart disease.”

“… Allows flexibility by removing the need to carry around temperate regulated medications so will be able to camp in the summer and winter. Go on vacation for longer than a couple of weeks.”

In terms of side effects, patients reported no or minor side effects with inclisiran, primarily temporary pain or swelling at the site of injection.

The following two patient profiles illustrates the ways in which inclisiran has impacted lives of patients with ASCVD.

Patient ED, Ontario

“I had a minor heart attack last November had two stents put in. There was a blockage of cholesterol. I had been on Crestor but couldn’t tolerate it so went to Lipitor, a very high dosage. I have had problem with high cholesterol all my life; my parents both had it and were on medication. I had a good diet with high fiber. But even on a very high Lipitor dosage, my cholesterol was not normal.

I lost my husband in 2017; he was an Alzheimer patient and caring for him probably took a toll on me.

I have now had two injections of inclisiran and my lab work shows my hemoglobin is down to normal. My nurse practitioner and cardiologist are very happy. I have had no reactions to Leqvio.

I am 83 years old and am feeling okay and fairly energetic. I do a lot of walking at the cottage.

Both of my sons on high dosage of statins, so I hope there is an option for them before they get a heart attack.

Patient RP, Alberta

“I am 48 years old with no family history of heart disease though my dad had very high blood pressure. I don’t usually go in for checkups; both of my parents are family physicians so I just relied on them.

But I was starting to get tired and decided to get a checkup. They came back and said the EKG looked funny and recommended more tests. But I was feeling fine, so put the tests off. Then a friend, who was also Indian and the same age, suddenly had a heart attack.

So, I decided to follow up with more tests. The doctor said I “almost needed a by-pass.” I took the EKG to a friend who was a surgeon, and he said, “I think you had a heart attack.”

I knew I had something. I am a dentist so have a medical background. It was post-COVID, and I was golfing and started sweating and felt faint. I went for run a run and was struggling but thought I was just out of shape.

My friend, the surgeon said he knew someone who could do the bypass but suggested starting with some drugs in the meantime. I started taking a statin (Crestor) but developed high liver enzymes.so switched to another statin (Lipitor). He also prescribed ezetimibe.

I don't know if high cholesterol runs in the family. I have two male cousins who were already on statins.

So I went back to the cardiologist who prescribe inclisiran. And my cholesterol is back to normal. I feel fine but am now very cautious."

7. Companion Diagnostic Test

The treatment would require a diagnosis of HoFH and perhaps identification of the specific deletions but these tests are not different from or additional to the diagnostic tests that are being carried out today to confirm the disorder. Moreover, there is no evidence that one form of HoFH responds better than another. Unlike the PCSK9s, it should work effectively across all deletion profiles.

8. Anything Else?

Patients living with ASCVD are realistic that Leqvio is not a cure; they will still be living at risk for high cholesterol and will need to do all the things recommended to reduce the risk of ASCVD. Many have a family history of high cholesterol. Nevertheless, many never get to see a specialist in a timely fashion and therefore, are never help.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

No outside help to complete submission.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No outside help to collect or analyze data, beyond receiving referrals from the clinicians.

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Novartis			X	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Durhane Wong-Rieger
Position: President & CEO
Patient Group: Canadian Organization for Rare Disorders
Date: 14 July 2023

Patient Input

Name of Drug: Inclisiran (Leqvio)

Indication: Primary hypercholesterolemia

Name of Patient Group: HeartLife Foundation

Author of Submission: Marc Bains

1. About Your Patient Group

An estimated 750,000 people are currently living with heart failure in Canada (Heart & Stroke Foundation, 2022). In their 2022 Report on the health of Canadians, the Heart & Stroke Foundation estimates that 100,000 Canadians are diagnosed with heart failure each year and this number is on the rise. Heart failure costs the Canadian healthcare system more than $2.8 Billion dollars per year – with the majority of those dollars being spent on acute care. Research has shown that effective patient engagement improves clinical outcomes, prevents hospitalizations, increases patient self-efficacy for managing their condition, and overall quality of life. Despite these findings, few organizations currently exist to help heart failure patients self-manage their condition, provide education and support for patients and families, and advocate for access to care and innovative treatments. The HeartLife Foundation was created in response to this need.

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. HeartLife Foundation is Canada's first – and only – national patient-led Heart Failure organization. We are a Federal Charity aimed at raising public awareness of Heart Failure, engaging patients, families, and caregivers to provide education and support, facilitate access to the latest research, innovations, and treatments, and advocate better care for all.

Founded in June 2016 by Dr. Jillianne Code, a heart failure survivor and heart transplant recipient, and Mr. Marc Bains, a heart failure survivor and heart transplant recipient, HeartLife aims to drive healthcare innovation and transformation by adding patient voices to the heart failure conversation. In collaboration with Dr. Sean Virani, one of Canada's leading heart failure specialists and promoter of patient and family centred care, we endeavour to ensure that there is an open dialogue including patients as partners with healthcare providers, government, and industry across Canada. Our members are all patients along the heart failure continuum, their families and caregivers.

Vision. To create a better everyday life for people living with heart failure.

Mission. 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.

Website: www.heartlife.ca

2. Information Gathering

The submission was completed by the patient partner executives of the HeartLife Foundation and includes data from literature review, one on one interviews with patients living with the disease, and study review.

3. Disease Experience

The Health consequences and impact of Atherosclerotic Cardiovascular Disease (ASCVD), such as Myocardial Infarctions, Ischemic Stroke, and Coronary Artery Disease (including unstable angina), have been extensively documented. These outcomes have significant implications for patients, caregivers, and the healthcare system.

A key factor that can be modified to mitigate the serious consequences of ASCVD is the control of blood lipids, particularly LDL-Cholesterol (LDL-C).

The prevalence and incidence of cardiovascular disease (CVD) in our country impose a substantial burden. ASCVD is recognized globally as a major non-infectious pandemic, and its adverse effects on Canadian families and the healthcare system are noteworthy. To improve health outcomes for patients, more comprehensive efforts are required to address CVD.

The immense number of individuals suffering from severe health complications due to ASCVD, such as heart attacks and ischemic strokes, as well as the significant mortality rates associated with CVD, underscore the urgent need to aggressively target the risk

factors of ASCVD using available tools and interventions. The product currently under review is one such valuable intervention that should be made widely accessible to Canadians.

The following are experts from interviews with patients living with ASCVD and high-levels of LDL Cholesterol:

Patient Partner #1 - *Managing a chronic condition like ASCVD is not easy. It was tough to stay motivated to take my medication and change lifestyle. There are so many medications and follow-ups. My numbers never changed.*

Patient Partner #2 - *Living with ASCVD can took a toll on my mental well-being patient's emotional well-being. That is often overlooked. Feelings of anxiety, depression, and fear of future heart events are always on my mind. Coping with these emotional challenges and maintaining a positive attitude is tough.*

Patient Partner #3 – *I was tired a lot. I had shortness of breath, chest pain, and fatigue. Exercising and engaging in physical activities and maintaining a normal routine was challenging.*

Patient Partner #4 – For me it was genetic. My dad passed away from it. So it's always on my mind. I think about me, my brothers, and my kids. It's tough mentally and physically.

Having a genetic disease can be challenging for families due to several reasons:

1. Emotional Impact: Discovering that a family member has a genetic disease can cause emotional distress and anxiety within the family. There may be feelings of sadness, fear, guilt, or anger, as family members grapple with the implications and potential limitations of the condition.

2. Uncertainty and Future Planning: Genetic diseases often come with uncertainty regarding the progression and severity of the condition. This uncertainty can make it challenging for families to plan for the future, including making decisions about healthcare, lifestyle adjustments, and long-term care arrangements.

3. Financial Burden: Genetic diseases can lead to significant financial burdens for families. Costs associated with medical consultations, specialized treatments, medications, assistive devices, therapies, and ongoing care can accumulate and put strain on family finances.

4. Impact on Relationships: Caring for a family member with a genetic disease can put a strain on relationships within the family. The demands of managing the condition, providing care, and dealing with the emotional aspects can create tension and stress, potentially affecting communication and dynamics between family members.

5. Genetic Testing and Decision-Making: Families may face difficult decisions regarding genetic testing for other family members, especially when it comes to assessing the risk of passing on the genetic disease to future generations. These decisions can be emotionally charged and require careful consideration of individual autonomy, privacy, and ethical considerations.

6. Stigma and Social Isolation: Some genetic diseases may carry social stigma, which can lead to isolation and challenges in social interactions. Families may find it difficult to navigate societal attitudes and perceptions surrounding the condition, which can impact their overall well-being and sense of belonging.

Despite these challenges, families often demonstrate resilience, support, and unity in facing genetic diseases together. Access to medications and seeking support can help families cope with the unique challenges associated with genetic diseases and promote their overall well-being.

4. Experiences With Currently Available Treatments

Numerous published evidence and authoritative clinical guidelines from reputable international advisory bodies consistently emphasize the importance of controlling LDL-C to reduce the risk of ASCVD and associated health consequences. Notably, the ORION trials (ORION-9, ORION-10, and ORION-11) demonstrated the effectiveness of inclisiran in lowering LDL-C levels in patients with heterozygous familial hypercholesterolemia (FH), atherosclerotic cardiovascular disease (ASCVD), or ASCVD-risk equivalents.

Existing treatment options for LDL-C management encompass fibrates, statins, ezetimibe, and PCSK9 inhibitors, among others. However, except for PCSK9 inhibitors, it is well-documented that many patients struggle to achieve target LDL-C levels with current therapies. A significant proportion of individuals treated with statins, for instance, are unable to attain desired LDL-C levels.

Moreover, patient adherence to currently available and publicly reimbursed therapeutic options is acknowledged to be poor. Although CADTH has recommended the public reimbursement of PCSK9 inhibitors due to their high efficacy, the accessibility of these

medications in Canada is limited. Provincial health benefit program reimbursement criteria impose strict restrictions on access for patients with uncontrolled LDL-C. Consequently, this limited access adversely affects the quality of life for individuals in need.

Below patient partners describe the challenges with current medical treatments:

Patient Partner #1 - *I did not like the current statin medication I was taking as it caused me pain and joint discomfort. Eventually, I reached a point where I couldn't tolerate it any longer. I actually stopped taking my medications. However, I had a heart attack during this period, but surprisingly, my joint pain disappeared.*

Patient Partner #2 – *I basically had an intolerance to my statins. I kept taking my medications and my numbers didn't change. There was really no way to improve my care anymore. It was a little depressing in fact. I kept taking the medications so I wouldn't get worse. But the side effects were tough. I was sore everywhere, all the time.*

Patient Partner #5 – *I thought I could tolerate most side effects. I actually think I had them all. The most significant one was muscle pain and weakness. Sometimes it was tough to handle. Well lots of times. Other side effects were digestive issues early on, increase in blood sugars, and I believe cognitive effects.*

Recent population-based studies conducted in Canada have revealed that a significant number of high-risk cardiovascular (CV) patients continue to have LDL cholesterol (LDL-C) levels well above the recommended threshold of 1.8 mmol/L, as outlined in the guidelines (Sud et al J Am Coll Cardiol 2020;76:1440-50; Sarak et al Circulation: Cardiovascular Quality and Outcomes 2021;14:e006646). This is attributed to various factors, including inadequate LDL-C reduction with statins (with or without ezetimibe), side effects associated with statin use, suboptimal medication adherence, and treatment disinterest.

5. Improved Outcomes

The desired outcome for Canadians is to minimize the long-term health consequences of ASCVD in high-risk patients by effectively managing LDL-C levels. Based on our current review, it is evident that Inclisiran demonstrates high efficacy in lowering LDL-C and serves as a suitable intervention for high-risk ASCVD patients who cannot achieve LDL-C control through diet and statins alone. Preliminary findings from clinical trials indicate that if Inclisiran is administered to 300,000 patients annually, it has the potential to prevent 55,000 heart attacks and strokes, potentially saving 30,000 lives over the next decade

The availability of a new treatment with improved accessibility and less frequent administration would be highly beneficial. This would enable more high-risk cardiovascular (CV) patients to achieve LDL cholesterol (LDL-C) levels below the recommended threshold. By achieving this goal, the occurrence of major adverse cardiovascular events, including myocardial (re-)infarction, ischemic stroke, the need for coronary revascularization, and cardiovascular death, would be significantly reduced.

The Canadian Cardiovascular Society Lipid Guidelines (Pearson et al Can J Cardiol. 2021;37:1129-1150) strongly recommend intensifying lipid-lowering therapy with a PCSK9 inhibitor, either with or without the additional use of ezetimibe, for secondary CV prevention patients who have shown the greatest benefit from PCSK9 inhibitor therapy. This recommendation applies to individuals whose LDL-C remains at 1.8 mmol/L and higher (or non-high-density lipoprotein cholesterol [non-HDL-C] at 2.4 mmol/L or higher, or apolipoprotein B [ApoB] at 0.7 g/L or higher) while receiving the maximum tolerated statin dose. These guidelines are based on numerous published subgroup analyses of CV outcome trials with PCSK9 monoclonal antibodies.Moreover, the convenience of a twice-yearly dosage schedule will reduce the pill burden and enhance patient adherence, leading to improved LDL-C control. This, in turn, may contribute to reducing the occurrence of significant ASCVD health outcomes such as ischemic stroke, ultimately enhancing the quality of life for individuals living with ASCVD.

Supervised injection of LDL-C treatment offers long-term benefits for managing LDL cholesterol levels, while also serving as an opportunity to reinforce other crucial aspects of cardiovascular risk reduction. This comprehensive approach allows for the integration of various elements such as maintaining a healthy diet, engaging in regular exercise, managing weight, and ensuring adherence to oral medications for lipid control, hypertension management, and diabetes. By utilizing supervised injection, patients can receive ongoing support in addressing all these essential factors, leading to improved cardiovascular health outcomes.

This therapy has proven effective in bringing LDL-C levels below the recommended threshold for the majority of these patients. However, many eligible patients are not receiving these agents due to significant barriers, primarily cost and limited access. It is important to note that these drugs are not covered for public reimbursement in Canada for patients with ASCVD.

6. Experience With Drug Under Review

All of the patient partners interviewed were currently on the drug under review. HeartLife was able to get unique and valuable insight from the patient partners. Excerpts from the interviews are below:

Patient Partner # 4- *I experienced a significant improvement in my overall well-being. My doctor confirmed that the results were much better, and I now enjoy a better quality of life without any side effects. It's worth noting that I only qualified for this new drug due to participating in a study. The drug has shown remarkable effectiveness, with a 75% reduction in ldl numbers. I firmly believe that this medication has the potential to save lives, and it should be covered and made accessible to those who need it.*

Patient Partner# 2- *The objective was to lower cholesterol levels, but not much more could be achieved through statins. Due to intolerance towards statins, experiencing undesirable side effects, my quality of life was adversely affected. However, finding an alternative solution allowed for better tolerance and fewer side effects, ultimately leading to reaching the target cholesterol levels. Nevertheless, the medication proved to be very expensive, making it unaffordable without coverage. The burden of paying out of pocket would have been substantial. Luckily, my doctor enrolled me in a special program. But I know this not available to all Canadians.*

Patient Partner # 5 - *Initially, there were concerns and hesitation due to a family history of cardiovascular issues. With a dad who passed away and a brother who underwent multiple open-heart surgeries at the age of 70, it was important to find a solution. The cost of the medication, at $6,000 per year I think, was steep, especially without any coverage. I have special coverage through a study. I started the medication on April 20th and being on the medication for 8 weeks, there have been significant positive changes. Within just 6 weeks, cholesterol levels improved remarkably. I haven't felt this good in years. The ease of the injection and absence of pill burden made the treatment process more manageable. Moreover, there has been a significant improvement in my mental well-being. Prior to starting inclisiran, maximum dosages of other medications failed to provide the desired results, leading to a sense of going to nowhere. The family doctor was happy to hear about these positive improvements.*

7. Companion Diagnostic Test

LDL cholesterol can be tested through a blood test called a lipid panel or lipid profile. This test is typically performed after a period of fasting, usually overnight, to obtain accurate results. The process involves a simple blood draw, where a healthcare professional collects a sample of blood, usually from a vein in the arm. It's important to note that LDL cholesterol testing is just one part of evaluating cardiovascular health. Healthcare providers may consider additional factors such as medical history, family history, and other risk factors to develop a comprehensive assessment of an individual's cardiovascular risk profile.

There are many factors to consider while fasting including: hunger and discomfort, energy and well-being. routine disruption, and blood sugar management.

8. Anything Else?

NA

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
BI				x
AZ				x
Novartis			x	
BMS			x	
Bayer			x	
Servier		x		

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Marc Bains
Position: Co-Founder
Patient Group: HeartLife Foundation
Date: **July 14, 2023**

Clinician Input

Clinician Group Input

CADTH Project Number: SR0791-000

Generic Drug Name (Brand Name: Inclisiran)

Indication: Primary hypercholesterolemia

Name of Clinician Group: Alberta Cardiovascular Disease Prevention Collaborative

Author of Submission: Sandeep Goel Aggarwal

1. About Your Clinician Group

Our group consists of a diverse set of individuals. This includes cardiologists and endocrinologists. We all have an interest in improving the heart health of our patients. See below for profiles.

1. Sandeep G. Aggarwal: Dr. Aggarwal is a cardiologist who has been in practice since 1998. He is a clinical professor of medicine at the University of Calgary and is the medical director of one of the largest cardiac rehabilitation programs in Canada (TotalCardiology Rehabilitation). He has insight into the issues regarding achieving secondary prevention goals and has published extensively on improving the heart health of patients after a cardiac event.

2. James A Stone, MD. PhD. Dr. Stone is a Clinical Professor of Medicine at the University of Calgary. He is the co-founder of the C-CHANGE (Canadian Cardiovascular Harmonization of National Guidelines Endeavour), which is in the only Canadian Clinical Practice Guideline endorsed by the Council of The Federation. He is the Lead Author on the Diabetes Canada Guidelines Chapter on Cardiovascular Protection and has been a member of the Canadian Cardiovascular Society Working Group on Hypercholesterolemia and Other Dyslipidemias since 2009.

3. Norman C W Wong, M.Sc, MD and FRCPC is a Professor of Medical Biochemistry and Medicine at the University of Calgary. He is a clinician investigator whose interests is in the area of dyslipidemia, cardiovascular risk, diabetes mellitus and studies epigenetics related to cardiovascular disease risks. He has published 173 peer reviewed manuscripts in connection with his research interest. His inclusion in this document arises from his work in the field of Familial Hypercholesterolemia (FH) and the Libin Clinic devoted to these patients was co-founded by him. Patients in the FH clinic who do not reach recommended goals in lowering of LDL need access to more options to lower their LDL.

4. Micha F Dorsch, MD. PhD. is an Interventional Cardiologist at the CK Hui Heart Centre in Edmonton and works at Edmonton Cardiology Consultants (ECC) (https://edmontoncardiology.com). His interest in this document arises from his work in secondary prevention at ECC. Together with colleagues he has developed a dedicated risk reduction clinic. Running this clinic taught us that more patient centered options are required to lower LDL and to achieve trial and guideline supported targets.

5. Jonathan G Howlett, MD FRCPC is a General and Advanced Heart Failure Cardiologist with a large General Cardiology practice, and extensive experience in Guideline Development (Heart Failure, Cardiac Transplantation, Care of CV Disease in the Elderly). He is involved in many Quality Improvement and Translational initiatives, and has published 197 articles in Peer Reviewed Medical Journals. His inclusion in this document arises from this work and his involvement as current Chair of the Canadian Cardiovascular Guidelines Committee and from the treatment of patients with limited access to care, where the learnings have shown a variety ot treatment delivery strategies are needed to improve the care of the largest number of people.

6. Robert C. Welsh, MD, FRCPC is a professor and academic interventional cardiologist at the Mazankowski Alberta Heart Institute and University of Alberta in Edmonton, Alberta, Canada. He is Co-chair of Vital Heart Response (STEMI regional reperfusion program). He is chair of the Canadian Cardiovascular Society PCI Quality Improvement working group. Clinical research interests are focused on the management of the full spectrum of coronary artery disease, acute coronary syndromes and interventional cardiology. Further research interests include secondary prevention, diabetes mellitus and cardiac physiology. He has published over 300 peer-reviewed articles, multiple book chapters and over 250 scientific abstracts. In collaboration with colleagues, he has received a Canadian Institute of Health Research-Canadian Medical Association Journal Top Canadian Achievements in Health Research Award.

7. Tyler Lamb, MD, MSc, FRCPC, FACC, DRCPSC. Dr. Lamb was born and raised in Saskatoon, Saskatchewan. He attended the University of Saskatchewan where he obtained his Bachelor of Science degree in Microbiology & Immunology in 2006, and his Doctor of Medicine degree in 2010. He remained at the University of Saskatchewan to complete his Internal Medicine and Cardiology residency training programs then relocated to Edmonton in 2016 for further clinical fellowship training in Echocardiography. Following his clinical fellowship, Dr. Lamb obtained his 'Diplomate of the Royal College of Physicians and Surgeons of Canada' designation in Echocardiography. He then went on to complete an echocardiography research fellowship under Dr. Harald Becher and concurrently completed a Master of Science degree in Translational Medicine. His area of study was 'Fusion 3D Echocardiography'.

8. Helen (Hailun) Shi Bsc. Pharm., APA., PharmD, CDE, CTE, CBE. Helen graduated from the University of Alberta Pharmacy Program in 2016 and then from the University of Alberta PharmD program in 2019. She's been a clinical pharmacist with Calgary COOP since 2018 and got her Certified Diabetes Educator certification in 2020, received her Certified Tobacco Educator in 2021, and her Certified Bariatric Educator in 2022. Her pharmacist role is a non dispensary and clinical work focus with additional training in Migraine Management, Osteoporosis, CV optimization, and Insulin Pumps.

2. Information Gathering

Our group has reviewed the literature on secondary prevention, specifically regarding the reduction of LDL. In addition Dr. Aggarwal did an analysis of his database of more than 20,000 patients to see how well patients can be managed in an active secondary prevention program where medication adjustments are made.

3. Current Treatments and Treatment Goals

Current Treatments and Treatment Goals

In the Canadian context, the current treatment paradigm for dyslipidemia or high cholesterol levels in patients with ASCVD (Atherosclerotic cardiovascular disease) and FH (Familial hypercholesterolemia) involves a combination of drug and non-drug interventions. The primary goal of treatment is to effectively manage cholesterol levels and reduce the risk of cardiovascular events. The following aspects should be considered when discussing the current treatment landscape:

Drug Treatments:

Statins: Statins are the cornerstone of pharmacological therapy for dyslipidemia. They work by inhibiting the enzyme HMG-CoA reductase, thus reducing cholesterol synthesis. Examples of commonly used statins in Canada include atorvastatin, simvastatin, and rosuvastatin. These medications have Health Canada approval and are supported by clinical practice guidelines. The trials include (4s, CARE, LIPID, HPS, IDEAL an TNT). These are over 56,000 patients.

Ezetimibe: Ezetimibe is often used in combination with statins to further lower LDL cholesterol levels. It works by inhibiting the absorption of cholesterol from the intestine. Ezetimibe is also approved by Health Canada and supported by guidelines.

PCSK9 inhibitors: These newer agents, such as evolocumab and alirocumab, are used as adjunctive therapy in patients with persistently elevated cholesterol despite maximal statin therapy or in those with familial hypercholesterolemia. They work by enhancing the clearance of LDL cholesterol receptors on liver cells. PCSK9 inhibitors are available in Canada through special access programs and are supported by guidelines. PCSK9 inhibitors (PSCK9i) offer significant morbidity and mortality benefits in the management of hypercholesterolemia. These potent therapies effectively lower LDL cholesterol levels by over 50%. Clinical trials consistently demonstrate that PSCK9 inhibitors, such as evolocumab and alirocumab, can substantially reduce the risk of major adverse cardiovascular events (MACE) by an impressive percentage. Studies have shown that treatment with PSCK9 inhibitors leads to a significant reduction in MACE, including heart attacks, strokes, and cardiovascular-related deaths, by up to 15%.

According to the FOURIER-OLE study, long-term treatment with evolocumab (Repatha; Amgen) is associated with a significant reduction in clinical outcomes, including cardiovascular mortality, compared with patients who delay starting PCSK9 inhibitor therapy1. Those who were originally treated with evolocumab had a 15% lower risk of major cardiovascular events and a 23% lower risk of cardiovascular death when compared with the placebo-treated patients who only switched to evolocumab once the parent trial was completed. The use of PSCK9 inhibitors as adjunctive therapy in high-risk patients who struggle to achieve optimal cholesterol control with conventional treatments holds great promise in improving patient outcomes and reducing the overall burden of cardiovascular disease. Unfortunately PSCK9 inhibitor therapies like evolucumab are very restricted in terms of access (both from public and private payors) such that many patients (especially those with ASCVD) don't have coverage for these agents that reduce both morbidity and mortality.

Other medications: In some cases, additional medications such as bile acid sequestrants (e.g., colesevelam) or fibrates (e.g., fenofibrate) may be considered, particularly for patients with specific lipid profiles or comorbidities. These drugs may have variable availability and support from clinical practice guidelines.

Non-drug Treatments:

Lifestyle modifications: Lifestyle interventions, including a heart-healthy diet, regular physical activity, weight management, and smoking cessation, form an integral part of cholesterol management. These interventions aim to reduce cholesterol levels and improve overall cardiovascular health.

Nutritional supplements: Certain nutritional supplements, such as plant sterols/stanols, omega-3 fatty acids, and soluble fibers, may also be recommended as adjuncts to lifestyle modifications. These supplements can help lower cholesterol levels, although their clinical effectiveness may vary.

Patient education and counseling: Patient education and counseling play a crucial role in promoting adherence to therapy, lifestyle modifications, and understanding the importance of cholesterol management.

Treatment Goals:

The ideal treatment for dyslipidemia or high cholesterol levels should aim to achieve the following goals:

Reduce LDL cholesterol levels: Lowering LDL cholesterol, particularly the LDL particle number or the non-HDL cholesterol fraction, has been consistently associated with a reduction in cardiovascular events. The LDL goal is to reduce the LDL to less than 1.8 in secondary prevention and by greater than 50% in patients with familial hypercholesterolemia (CCS 2021 dyslipidemia guidelines). For instance, a meta-analysis of randomized controlled trials involving over 90,000 patients showed that every 1 mmol/L reduction in LDL cholesterol was associated with a 22% relative risk reduction in major cardiovascular events among individuals with a history of cardiovascular disease. There is no lower number of achieved LDL where the reduction of events in secondary prevention where there is attenuation of the benefit. In other words the lower you go the better it is in terms of benefit.

Modulate other lipid parameters: Treatment should also address other lipid abnormalities, including triglyceride levels, HDL cholesterol levels, and the overall lipid profile.

Prevent cardiovascular events: The ultimate goal is to reduce the risk of cardiovascular events, such as heart attacks and strokes, through effective cholesterol management.

Improve health-related quality of life: Treatment should enhance the patient's overall well-being, reduce symptoms related to dyslipidemia, and improve their ability to maintain employment and independence.

Minimize adverse effects: An ideal treatment should prioritize a favorable safety profile, minimizing side effects and drug interactions. While statin therapies have demonstrated efficacy, it is important to acknowledge that they can be associated with side effects in up to 20% of patients, leading to dose reduction or discontinuation of therapy, potentially increasing the risk of cardiovascular events. In contrast, PCSK9 therapies, such as evolocumab and Inclisiran, offer a more favorable side effect profile and higher tolerability, which significantly improves the likelihood of patients adhering to these medications. As a result, these therapies have shown a notable reduction in cardiac events.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Non-responsiveness to current treatments: Despite receiving optimal therapy, a significant proportion of patients with hypercholesterolemia do not achieve the recommended LDL cholesterol targets. Studies have reported that approximately 20-30% of patients may be classified as "statin non-responders," as they do not adequately respond to statin therapy in terms of achieving target LDL cholesterol levels.

Treatment refractoriness: Over time, some individuals may develop a refractory response to statin therapy. For example, studies have indicated that up to 10-15% of patients on statin treatment may experience persistent high LDL cholesterol levels, even with dose optimization and adherence to therapy. Currently in the Canadian context we know using large databases in Alberta that 1/3 of patients are not at their LDL target after one year of therapy (Chen, CJC 2019) . In the TotalCardiology Rehabilitation database we are able to show that with aggressive secondary prevention programs that we can reduce this gap in therapy to 20%. Realistically we should be able to reduce this to < 10% with the addition of PCSK9 therapies.

Disease reversal: Currently available therapies primarily focus on LDL cholesterol reduction and reducing the risk of cardiovascular events. While they have shown benefits in terms of event reduction, there are no approved treatments that can actively reverse the underlying atherosclerotic disease process. The reduction of LDL cholesterol has been consistently shown to have a profound impact on cardiovascular health, with evidence suggesting that it can lead to plaque regression and improved outcomes. Multiple studies, including those conducted with statin therapies and PCSK9 inhibitors, provide compelling data supporting this effect. For instance, the landmark Glagov trial demonstrated that intensive LDL reduction with statins resulted in coronary plaque regression, as assessed by intravascular ultrasound (IVUS). Moreover, reductions in LDL cholesterol have been associated with decreased intima-media thickness (IMT), a marker of atherosclerosis progression, further supporting the mechanistic link between LDL reduction and improved cardiovascular outcomes. These findings underscore the importance of aggressively targeting LDL cholesterol levels to not only prevent plaque progression but also to induce plaque regression, ultimately reducing the risk of cardiovascular events in high-risk individuals.

Limited treatment options for specific outcomes: While statins are effective in reducing LDL cholesterol, there is a need for targeted therapies to further reduce LDL as even the strongest statins only reduce LDL by 45%. In many patients this is inadequate to achieve the risk reductions that could be achieved with much lower LDL as these patients remain above the targets for therapy.

Treatment tolerability: Adverse events associated with statin therapy can impact treatment tolerability and adherence. Common side effects include muscle-related symptoms, liver enzyme abnormalities, and, rarely, the development of diabetes. These adverse events may lead to treatment discontinuation or dose reduction, potentially compromising the effectiveness of therapy. On the other hand treatment with PCSK9 therapies have few side effects and are generally well tolerated aside from local site injection reactions.

Compliance improvement: Studies have shown that long-term adherence to statin therapy is suboptimal, with a significant proportion of patients discontinuing or not adhering to treatment regimens. For example, adherence rates as low as 30-50% have been reported in some patient populations, highlighting the need for interventions to improve compliance. Although there is no data in the field of dyslipidemia, in the treatment of DM, the option of changing from daily administration of GLP-1RA to weekly improved compliance by 11%.

The unique dosing regimen of Inclisiran, a twice-yearly injectable PCSK9 inhibitor, holds the potential for improved compliance compared to daily oral medications. Evidence from other therapeutic areas, such as diabetes management, suggests that therapies with infrequent injections, such as once-weekly or less frequent, may enhance adherence and persistence. Studies have shown that patients receiving long-acting injectable medications, including GLP-1 receptor agonists and once-weekly insulin, exhibit higher compliance rates and improved treatment satisfaction. By requiring only two injections per year, Inclisiran offers a convenient and simplified treatment approach that may contribute to better compliance, reducing the burden of daily medication intake and potentially improving long-term patient outcomes. While direct evidence specific to Inclisiran is currently limited, these findings suggest a promising potential for enhanced compliance with the less frequent injection regimen of Inclisiran. The potential to increase adherence to LDL lowering therapy will hopefully translate to reduced MACE events in the population.

Convenience of formulations: The currently available formulations of lipid-lowering medications may have limitations in terms of administration, dosing frequency, or convenience of use. For example, some medications require daily dosing or have specific instructions regarding food intake, which may impact patient acceptance and adherence.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

The drug under review, Inclisiran, would potentially fit into the current treatment paradigm as an innovative addition to existing therapies for managing dyslipidemia and reducing LDL cholesterol levels. With its unique mechanism of action utilizing RNA silencing technology, Inclisiran complements other available treatments by targeting specific genes involved in cholesterol synthesis, which is distinct from the mechanism of statins or other traditional lipid-lowering therapies. It is expected to be used in combination with other treatments rather than as a standalone therapy.

While Inclisiran is not the first treatment approved to address the underlying disease process of dyslipidemia, it represents an advancement in the management of the condition by offering a different approach to lowering LDL cholesterol levels. It targets the genetic component involved in cholesterol production, potentially providing an additional option for patients who do not adequately respond to or tolerate other therapies.

The placement of Inclisiran in the treatment algorithm would depend on several factors, including its safety profile, efficacy, and cost-effectiveness. It would be considered as a later-line treatment option for patients who have not achieved optimal LDL cholesterol reduction with standard therapies or for those who experience intolerance or contraindications to other treatments. We expect that all patients would be on maximally tolerated lipid lowering therapy that would at minimum include the highest tolerated statin therapy.

We expect that at most 20% of patients with ASCVD would fit the criteria for treatment. Similarly 20-30% of patients with FH would also not achieve LDL targets and may be considered for PCSK9 therapies.

The introduction of Inclisiran is expected to cause a shift in the current treatment paradigm by providing an alternative approach to LDL reduction. It offers a unique mechanism of action that may address unmet needs, such as non-responsiveness to other treatments or intolerance to traditional therapies. We expect that PCKS9i therapies to still be used (such as evolocumab) where there is appropriate coverage for that agent however Inclisiran is less expensive and may save the health care system if this agent is used instead of PCSK9i therapies which have a higher cost per year. The hope is that this savings could be used to fund the less expensive options such as Inclisiran to treat a wider group of patients which would improve the vascular health of more patients.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Patients most likely to respond: Patients who are most likely to respond to treatment with Inclisiran are those with elevated LDL cholesterol levels, particularly individuals with ASCVD or familial hypercholesterolemia (FH) who have not achieved their LDL cholesterol goals despite statin therapy.

Most in need of intervention/ identification of patients: Patients with atherosclerotic cardiovascular disease (ASCVD) are at a significantly high risk of recurrent events, making intervention crucial. These individuals face a greater than 30% chance of experiencing events within the next 10 years, emphasizing the need for aggressive treatment. Certain subgroups within the ASCVD population stand to gain the most from intervention, including those with recent myocardial infarction, recurrent cardiac events, atherosclerotic disease affecting multiple vascular territories (ex peripheral arteries, carotid arteries, coronary arteries), diabetes, familial hypercholesterolemia (FH), and those requiring coronary artery bypass surgery or stents in multiple arteries. FH patients, in particular, have a significantly elevated lifetime risk of early heart disease, with some experiencing heart disease as early as their 30s. Early treatment is imperative to improve their lifespan and reduce the risk of premature heart disease. However, many FH patients do not respond well to statin therapy due to the specific genetic defect underlying their condition. ASCVD patients with the above conditions whose LDL is > 1.8 mmol/L would be the ones who would benefit the most. This would identify these patients for treatment.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Outcome assessment: In clinical practice most clinicians would monitor the lipid parameters as a surrogate to the risk of cardiac events. After Inclisiran therapy LDL should be assessed 6 weeks after initiating therapy and then yearly afterwards to ensure compliance and effectiveness. Since achieved LDL correlates tightly with outcome benefits this would be sufficient in most community settings. In specific university settings it would be expected that large databases would assess the effectiveness of therapy by looking retrospectively at cardiac events (myocardial infarction, angioplasty, bypass surgery, cardiovascular mortality) and attempting to correlate with changes in therapy using cohort data.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

There are several indications for discontinuing Inclisiran therapy that should be considered in clinical practice. These indications may include:

1. Severe hypersensitivity or allergic reactions: If a patient develops a severe allergic reaction or hypersensitivity to Inclisiran, discontinuation of the therapy is warranted.

2. Significant adverse events: In the presence of severe adverse events or complications associated with Inclisiran therapy, discontinuation may be necessary. Adverse events should be carefully evaluated, and the decision to discontinue treatment should be based on the individual patient's clinical status and the severity of the adverse events.

3. Unmanageable side effects: If a patient experiences persistent and unmanageable side effects that significantly impact their quality of life or ability to adhere to the treatment regimen, discontinuation of Inclisiran therapy may be considered.

4. Patient preference or non-adherence: If a patient expresses a strong preference to discontinue Inclisiran therapy or is consistently non-adherent to the treatment regimen, discontinuation may be appropriate. Patient engagement and shared decision-making should guide this decision, considering the potential impact on cardiovascular risk and alternative treatment options.

5. Lack of clinical benefit: In cases where Inclisiran fails to achieve the desired therapeutic response or fails to sufficiently reduce LDL cholesterol levels despite an adequate trial period, discontinuation may be considered. This decision should be

made in consultation with the healthcare provider and may involve reassessing treatment goals and considering alternative treatment options.

From the clinical trial the frequency of adverse events were similar to placebo except for: Inclisiran injection site reaction (■), injection site pain (■), injection site erythema (■), and injection site rash (■). Given the low frequency of adverse events we don't expect that the above reasons for discontinuation will occur frequently in clinical practice in the real world.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

We expect Inclisiran to be ordered in the community setting by specialists in internal medicine, endocrinology and cardiology. It would be less commonly ordered by primary care or other specialists. This is similar to what we currently see with PCSK9i therapy where specialists form the vast majority of initial prescriptions. Support of nursing, pharmacy and allied health will ensure success in the delivery of the medication. Many of us have already created partnerships to ensure that the delivery of this type of medication is done safely, on time and therefore result in the greatest benefit to patients.

6. Additional Information

Is there any additional information you feel is pertinent to this review?

Inclisiran belongs to a new class of medications for use in human disease states. It is one of the first siRNA therapies that will be used in a population with a common problem but a deadly one which kills many Canadians. The more options available for treating these patients will save the lives for more Canadians.

Availability of inclisiran would also increase patient choice. It is our initial experience with this drug that select patients who have been reluctant to self inject with a PCSK-9 inhibitor every two weeks are agreeable to twice yearly injections by a health-care professional. We believe that offering this additional option would allow for greater patient choice and contribute to patient centered healthcare.

Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

No help from outside our clinician group was obtained.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

No help was obtained outside our clinician group.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

No financial payments were provided to the Alberta Cardiovascular Disease Prevention Collaborative group however individuals within the group have declared their individual declarations below.

Declaration for Clinician 1

Name: Sandeep Aggarwal

Position: Medical Director, TotalCardiology Rehabilitation

Date: 11-07-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis		x		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: James A. Stone, Md, PhD, FRCPC, FAACVPR, FACC

Position: Clinical Professor of Medicine, UNiversity of Calgary

Date: 07/07/2023

☒I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis		xx		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Norman C W Wong

Position: Professor of Medical Biochemistry and Molecular Biology

Date: 08/07/2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis		xx		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Dr Micha F Dorsch

Position: Cardiologist

Date: 09-07-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Jonathan G Howlett

Position: Cardiologist

Date: 07-10-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis		x		
Amgen	x			
AstraZeneca	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Robert C. Welsh t

Position: Cardiologist

Date: 07-10-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 6: Conflict of Interest Declaration for Clinician 6

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis		x		
BMS	X			
Bayer			X	
AstraZeneca	x			

Declaration for Clinician 7

Name: Tyler Lamb

Position: Cardiologist

Date: 10/07/2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 7: Conflict of Interest Declaration for Clinician 6

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	X			
BMS	X			
Bayer	X			
AstraZeneca	x			

Declaration for Clinician 8

Name: Helen (Hailun) Shi Bsc. Pharm., APA., PharmD, CDE, CTE, CBE.

Position: Clinical Pharmacist with Calgary CO-OP

Date: 07/11/2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 8: Conflict of Interest Declaration for Clinician 8

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Amgen Canada	x			
Abbot,	x			
Ascensia	x			
Assertio	x			
AstraZeneca	x			
Becton	x			
Dexcom	x			
Dickinson and Company	x			
Eli Lilly	x			

Novo Nordisk	x			
Novartis	x			
GlaxoSmithKline	x			

Clinician Group Input

CADTH Project Number	**SR0791-000**
Generic Drug Name (Brand Name)	**Inclisiran**
Indication	As per the Health Canada approved indication, for primary hypercholesterolemia (Heterozygous familial hypercholesterolemia (HeFH) and non-familial hypercholesterolemia (nFH)) with atherosclerotic cardiovascular disease (ASCVD).
Name of the Clinician Group	**BC Lipid specialists**
Author of the Submission	**Dr. Liam Brunham, MD, PhD, FRCP, FACP, FNLA**
Contact information	Name: Liam Brunham Title: Medical Lead, Healthy Heart Program Prevention clinic, St. Paul's Hosp., Associate Professor, University of British Columbia Email: [redacted] Phone: [redacted]

1. About Your Clinician Group

This is an informal group consisting of the 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, the Victoria Lipid Clinic and the Vascular risk & Prevention clinic at Royal Jubilee Hospital. Our group shares best practices, collaborates on research and educational projects and meets through various forums including conferences, CME and other events.

2. Information Gathering

Review of relevant literature, conference presentations, clinical experience with inclisiran since its release in Canada and background knowledge in the area. Several members of our group now have substantial experience in the clinical use of inclisiran in our lipid clinics.

3. Current treatments
3.1. Describe the current treatment paradigm for the disease
Response: Currently Health Canada-approved treatments include statins, ezetimibe and PCSK9 monoclonal antibodies, in addition to dietary therapy consisting of reducing saturated fat intake and dietary cholesterol. All of these therapies are routinely used in clinical practice and endorsed in the 2021 Canadian Cardiovascular Society dyslipidemia guidelines. Other medications such as fibrates are not indicated for LDL-C lowering and do not reduce CV risk. Bile acid resins are seldom used due to poor tolerance and poor LDL-C lowering properties and little evidence for CV risk reduction is available.
4. Treatment goals
4.1. What are the most important goals that an ideal treatment would address?
Response:

An ideal treatment would reduce levels of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels as much as possible, reduce the risk of major adverse cardiovascular events and cardiovascular mortality, and be safe and well tolerated and have properties that promote adherence.

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Response:

1. Tolerability. Many patients perceive side-effects to statins and ezetimibe, leading to therapy discontinuation. Therapies with lower rates of perceived side-effects are needed.
2. Compliance. Agents that optimize patient adherence to treatment are needed. It is well known that daily dosing regimens are seldom adhered to fully.
3. Treatment to target. Despite existing therapies, many patients do not reach their guideline-recommended lipid target. This issue is increasing in importance because the latest version of many guidelines (including the 2020 Canadian Cardiovascular Society lipid guidelines) recommend treating LDL-C to even lower levels in high risk patients. Add-on therapies are therefore needed to allow patients to reach their lipid targets.
4. Accessibility. Due to the high cost of PCSK9 inhibitors, and the lack of coverage for the ASCVD indication in all Canadian provinces, therapies with greater accessibility to the large population of patients that would be benefit by virtue of their high CV risk are needed. Additionally, many patients with FH who have a high, lifelong CV risk, may require access to alternatives to PCSK9 inhibitors.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Response:

1. Heterozygous FH
2. Patients with statin intolerance
3. Patients with ASCVD with other markers of high risk, including: recent MI, CABG, multi-vessel disease, polyvascular disease, diabetes, elevated Lp(a)

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

Response:

The drug under review works by inhibiting PCSK9 synthesis, thereby diminishing liver excretion into the circulation and subsequently increasing the expression of hepatic LDL receptors. Thus, inclisiran ultimately works through a common mechanism with other approved lipid lowering therapy with proven ability to lower CV risk safely. It would be the first siRNA drug in class. It would be most likely used as an add-on to maximally tolerated doses of statins (and/or ezetimibe) in patients who require additional lipid lowering.

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

Response:

Statins are likely to remain the cornerstone of therapy for these patients given the amount of data supporting them, and as such the drug would most likely be used after a patient has already been optimized and is taking their maximally tolerated statin dose (which may be no statin in a fully statin-intolerant patient). Alternative LDL-C lowering add-on drugs may sometimes be effective if LDL-C levels are close to optimal levels (i.e. use of ezetimibe) whereas when residual LDL-C remains high, the most appropriate statin add-on would have to be more potent (e.g. PCSK9 inhibitor or inclisiran).

6.3. How would this drug affect the sequencing of therapies for the target condition?

Response:

It may displace PCSK9 inhibitors as an add-on to statins and ezetimibe if it is more accessible and depending on the results of currently ongoing CV outcome trials. It may also fill a void if approved for high- risk secondary prevention patients.

6.4. Which patients would be best suited for treatment with the drug under review?

Response:

Based on available data the response to the drug is highly uniform, and as such it would be suited to all patients who require additional LDL lowering. But in particular, wherein either lifetime or short-term CV risk is high, patients especially suited are those requiring secondary ASCVD prevention, patients with FH and patients with high risk such as those with DM or high Framingham Risk Score.

6.5. How would patients best suited for treatment with the drug under review be identified?

Response:

Patients would be identified based on their diagnosis (FH or ASCVD) and the results of lipid testing (LDL-C, non-HDL-C, apoB). These tests are widely available and used in practice. For patients with FH specifically, there is a large degree of underdiagnosis, with only ~15% of patients with this condition identified in Canada. There is an ongoing need to improve the identification of patients with FH. Patients who are asymptomatic should be treated in specific circumstances: 1) patients with FH, 2) patients with documented atherosclerotic disease who have not yet had a clinical event and other guideline-recommended patient groups considered to have high CV risk amenable to the benefits of LDL-C lowering (e.g. high Framingham Risk Patients, patients with DM and patients with chronic kidney disease).

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

1. Patients who do not have an indication for the therapy
2. Patients who have achieved LDL targets on other therapies
3. Patients who have not attempted a statin

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

Response:

Based on available data and waterfall plots, the response to the drug is fairly uniform, and therefore the issue of non-response is likely not particularly relevant. There may be 'hyper-responders', but it is not likely to be practical or necessary to identify such patients prior to treatment. In theory patients with a PCSK9 gain-of-function mutation have been shown to have a greater than average response, but they represent a very small percentage of patients and genetic testing for this is not clinically warranted.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Response:

LDL-C, non-HDL-C, and ApoB measurements all align with typical clinical practice and are endorsed by national guideline recommendations.

6.9. What would be considered a clinically meaningful response to treatment?

Response:

At least a 30% reduction in LDL-C or non-HDL-C would be considered meaningful.

6.10. How often should treatment response be assessed?

Response:

At least every 6 months when beginning therapy. Possibly every year once on stable treatment.

6.11. What factors should be considered when deciding to discontinue treatment?

Response:

Lack of response (expected to be very rare); intolerability; other treatment becomes more accessible/available (eg PCSK9 inhibitor).

6.12. What settings are appropriate for treatment with the drug under review?

Response:

Specialty clinic, community setting, hospital or community outpatient clinic.

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

If so, which specialties would be relevant?

Response:

In theory this drug should be able to be appropriately used by both primary care and specialist physicians. In practice, FH is infrequently diagnosed in primary care, so identification of these patients may require a specialist familiar with this. Many ASCVD patients are followed by a specialist (internist, cardiologist, etc), and it is expected this would be the most likely scenario in which the drug would be initiated.

7. Additional information

7.1. Is there any additional information you feel is pertinent to this review?

Response:

Our group provided input when this drug was initially reviewed by CADTH in 2021, but there was little indication of how our input was used in the final decision rendered by CADTH, and some aspects of our input appeared to be misinterpreted. We look forward to engaging with CADTH on this submission and to learning how clinician input is incorporated into the final decision.

Since the time of our previous submission, the clinical trial data in support of inclisiran has strengthened considerable, with longer term safety and efficacy data which provide a more robust evidentiary basis for this molecule. In addition, several members of our group have accumulated significant clinical experience with the use of inclisiran since it became commercially available in Canada. This experience has reinforced our view, based on both clinical experience and the best available data, that inclisiran represents an important option for Canadian patients who do not achieve recommended levels of LDL cholesterol on currently available therapies, and is therefore an important tool for this large group of high risk patients.

Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

No.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Clinician Information	
Name	*Liam Brunham*
Position	*Associate Professor, UBC; Medical Lead, Healthy Heart Program Prevention Clinic, St. Paul's Hospital*
Date	*July 12, 2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Amgen	☒	☐	☐	☐
Novartis	☒	☐	☐	☐
HLS	☒	☐	☐	☐
Ultragenyx	☒	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*G B John Mancini*
Position	*UBC Professor, Director, CardioRisk Clinic (Vancouver Hospital), Staff Physician Healthy Heart Program Prevention Clinic (St. Paul's Hospital)*
Date	*July 12, 2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration	
Company	**Check Appropriate Dollar Range**

	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Amgen	☐	☒	☐	☐
Sanofi	☐	☒	☐	☐
Novartis	☒	☐	☐	☐
HLS Therapeutics	☐	☒	☐	☐
Esperion	☒	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*Carolyn Margaret Taylor*
Position	*Associate Professor, UBC, Medical Director, Cardiac Rehabilitation Program, St Paul's Hospital*
Date	*July 12, 2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Amgen	☒	☐	☐	☐
Novartis	☒	☐	☐	☐
Sanofi	☒	☐	☐	☐
Astra Zeneca	x			

Declaration for Clinician 4

Clinician Information	
Name	*Christopher Franco*
Position	*UBC Clinical Assistant Professor, Medical Lead CCU, Staff Cardiologist Royal Jubilee Hospital, Victoria BC*
Date	*July 12, 2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Bayer	☒	☐	☐	☐
Amgen	☒	☐	☐	☐
Novartis	☒	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Peter Tan*
Position	*Clinical Assistant Professor (UBC). Cardiologist Surrey Memorial Hospital. Consultant Lipid Clinic, Jim Pattison Outpatient Care and Surgery Centre*
Date	*July 12, 2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Amgen	☒	☐	☐	☐
Sanofi	☒	☐	☐	☐

Declaration for Clinician 6

Clinician Information	
Name	*Gordon Hoag*
Position	*UBC Professor, Division Head Medical Biochemistry, VIHA, Director and Staff Lipidologist, Victoria Lipid Clinic, Victoria, BC*
Date	*July 12, 2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Sanofi	☐	☐	☒	☐
Amgen	☒	☐	☐	☐
Novartis	☒	☐	☐	☐

Declaration for Clinician 7

Clinician Information	
Name	*Gordon Francis*
Position	*Professor of Medicine, University of British Columbia; Physician, Healthy Heart Program Prevention Clinic, St. Paul's Hospital, Vancouver, BC*
Date	*July 12, 2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range

	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
N/A	☐	☐	☐	☐

Declaration for Clinician 9

Clinician Information	
Name	*Michael Chen*
Position	*UBC Clinical Assistant Professor, Consulting physician, Victoria Lipid Clinic, Victoria BC*
Date	*July 12, 2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AMGEN	☒	☐	☐	☐

Declaration for Clinician 10

Clinician Information	
Name	*Apoorva Bollu*
Position	*UBC Clinical Assistant Professor, Consulting physician, Surrey Lipid Clinic*
Date	*July 12, 2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AMGEN	☒	☐	☐	☐
Sanofi	☒	☐	☐	☐

Declaration for Clinician 11

Clinician Information	
Name	*Iulia Iatan*
Position	*Consulting physician, Healthy Heart Program, St. Paul's Hospital*
Date	*July 12, 2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**

N/A	☐	☐	☐	☐
Sanofi	☒	☐	☐	☐

Clinician Group Input

CADTH Project Number: SR0791-000

Generic Drug Name (Brand Name): Inclisiran

Indication: Inclisiran is indicated in adults with primary hypercholesterolemia (heterozygous familial and non-familial), as an adjunct to diet: • in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach low density lipoprotein cholesterol (LDL-C) goals with the tolerated dose of a statin or, • alone or in combination with other lipid-lowering therapies.

Name of Clinician Group: Cambridge Cardiac Rehab Program

Author of Submission: A. Shekhar Pandey

1. About Your Clinician Group

Cambridge Cardiac Rehab Program is the regional cardiac rehabilitation and prevention program for Cambridge and North Dumfries and surrounding region of Cambridge, Ontario. This not for profit program represents the health care providers providing high risk primary and secondary cardiovascular prevention services for our region. Our group frequently communicates to share best practices, collaborates on research and educational projects and meets through various forums including advisory board, conferences, CME and other events.

2. Information Gathering

Review of relevant literature and publications, expert opinion gathering as well as background knowledge in the area

3. Current Treatments and Treatment Goals

Currently Health Canada-approved treatments for cholesterol reduction and ASCVD prevention include statins, ezetimibe and PCSK9 monoclonal antibodies, bile acid sequestrants, in addition to dietary therapy consisting of reducing saturated fat intake and dietary cholesterol. All of these therapies are used in clinical practice as per the 2021 Canadian Cardiovascular Society (CCS) dyslipidemia guidelines. Other medications such as fibrates are not indicated for LDL-C lowering and do not reduce CV risk.

4. Treatment Gaps (unmet needs)

Despite the availability of these treatments, a significant percentage of patients at risk for ASCVD fail to achieve the targets for LDL as out lined in the CCS 2020 guidelines. This is in part due to failure of these agents to achieve the low LDLs required, side effect profile / tolerability and patient adherence due to complexity of some medication regimens like bi-monthly PCSK9 inhibitor antibody injections patients are expected to self administer.

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

1. Tolerability. Many patients perceive side-effects to statins and ezetimibe, leading to therapy discontinuation. Therapies with lower rates of perceived side-effects are needed.
2. Compliance. Agents that optimize patient adherence to treatment are needed. It is well known that daily dosing regimens are seldom adhered to fully. Similarly complex regimens that require patients to self administer injectable agents twice monthly are often forgotten and missed dosing results in sub-optimum lipid control.
3. Treatment to target. Despite existing therapies, many patients do not reach their guideline recommended lipid target. This issue is increasing in importance because the latest version of many guidelines (including the 2020 Canadian Cardiovascular Society lipid guidelines) recommend treating LDL-C to even lower levels in high risk patients. Add-on therapies are therefore needed to allow patients to reach their lipid targets.
4. Accessibility. Due to the high cost of PCSK9 inhibitors, and the lack of coverage for the ASCVD indication in all Canadian provinces, therapies with greater accessibility to the large population of patients that would be benefit by virtue of their high CV risk are needed. Additionally, many patients with FH who have a high, lifelong CV risk, may require access to alternatives to PCSK9 inhibitor antibody therapies if they are intolerant to them.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

The drug under review works by inhibiting PCSK9 synthesis, thereby diminishing liver excretion of the PCSK9 protein into the circulation. PCSK9 protein results in the degradation of LDL receptors on hepatocytes. By reducing circulating PCSK9 protein, the drug under review subsequently increases the density of hepatic LDL receptors. Thus, inclisiran ultimately works through a common mechanism with other approved lipid lowering therapy with proven ability to lower CV risk safely. It would be the first siRNA drug in class. It would be most likely used as add-on to maximally tolerated doses of statins (and/or ezetimibe) in patients who require additional lipid lowering to achieve CCS 2021 LDL guidelines. It would not be used in combination with currently available antibody based PCSK9 inhibitors like alirocumab and evolocumab that work through similar PCSK9 pathways. It's uniqure twice yearly administration makes it particularly attractive for needle phobic patients where Alirocumab and evolocumab are challenging to use as they require twice monthly injections. As well, there are some patients who have adverse reactions or intolerant to antibody based PCSK9 inhibitors. In our own program, in the limited time that Inclisiran has been available for use in Canada, we have had 3 such patients that were either intolerant to or had adverse reactions to monoclonal antibody based PCSK9 inihibitors and were switched to Inclisiran with good response and tolerability to date.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Which patients are most likely to respond to treatment with drug under review?

1. Patients with ASCVD with other markers of high risk, including: recent MI, CABG, multi-vessel disease, polyvascular disease, diabetes, elevated Lp(a).
2. Heterozygous FH
3. Patients with statin intolerance

Which patients are most in need of an intervention?

Based on available data the response to the drug is highly uniform, and as such it would be suited to all patients who require additional LDL lowering. But in particular, wherein either lifetime or short-term CV risk is high, patients especially suited are those requiring secondary ASCVD prevention, patients with FH and patients with high risk such as those with DM or high Framingham Risk Score. This includes:

1. Patients with ASCVD with other markers of high risk, including: recent MI, CABG, multi-vessel CAD, peripheral vascular disease patients, polyvascular disease, diabetes, and elevated Lp(a)
2. Heterozygous FH
3. Patients with partial statin tolerance that are unable to tolerate maximum dose statins and do not achieve target LDLs at the lower doses of statins that they do tolerate.

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

Patients not at target for LDL per CCS guidelines 2021 will benefit if they are on maximally tolerated statins +/- Ezetrimibe.

How would patients best suited for treatment with drug under review be identified (e.g., clinician examination/judgement, laboratory tests (specify), diagnostic tools (specify))

Patients would be identified based on their diagnosis (FH or ASCVD) and the results of lipid testing (LDLC, non-HDL-C, apoB). These tests are widely available and used in practice routinely.

Are there any issues related to diagnosis?

No.

Is a companion diagnostic test required?

LDL measurement when on therapy with maximally tolerated statins +/- Ezetrimibe

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

A significant number of high risk patients are not adequately identified in clinical practice due in part to a sense of futility since there have not been effective alternate therapies. For patients with FH specifically, there is a large degree of underdiagnosis, with only ~15% of patients with this condition identified in Canada. There is an ongoing need to improve the identification of patients with FH.

Is it possible to identify those patients who are most likely to exhibit a response to treatment with drug under review?

Not that we are aware of. Based on available data, the response to the drug appears fairly uniform, and therefore the issue of non-response is likely not particularly relevant. In theory patients with a PCSK9 gain-of-function mutation have been shown to have a greater than average response, but they represent a very small percentage of patients and genetic testing for this is not clinically warranted.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Are outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

LDL-C, non-HDL-C, and ApoB measurements all align with typical clinical practice and are endorsed by national guideline recommendations.

What would be considered a clinically meaningful response to treatment? Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

At least a 30% reduction in LDL-C or non-HDL-C would be considered meaningful.

Examples: improved survival; reduction in the frequency/severity of symptoms (provide specifics regarding changes in frequency, severity, etc.); attainment of major motor milestones; ability to perform activities of daily living; improvement of symptoms; and stabilization (no deterioration) of symptoms.

Reductions in levels of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels have been shown to reduce the risk of major adverse cardiovascular events and cardiovascular mortality.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Examples: disease progression (specify, e.g. loss of lower limb mobility); certain adverse events occur (specify type/frequency/severity); or additional treatment becomes necessary (specify).

At least a 30% reduction in LDL-C or non-HDL-C would be considered meaningful. If a smaller reduction is noted, this may be a reason to re-evaluate the appropriateness of continuing this therapy.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

If a specialist is required, which specialties would be relevant?

Specialty clinic, community setting, hospital or community outpatient clinic. This should not require a specialist consultation as LDL is measured routinely in primary care facilities. This drug should be able to be appropriately used by both primary care and specialist physicians. In practice, FH is infrequently diagnosed in primary care, so identification of these patients may require a specialist familiar with this. Many ASCVD patients are followed by a specialist (internist, cardiologist, etc), and it is expected this would be the most likely scenario in which the drug would be initiated.

6. Additional Information

Is there any additional information you feel is pertinent to this review?

Additional therapies to effectively lower LDL cholesterol are required to improve patient outcomes including reductions in ASCVD events and mortality.

Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

   None.

Declaration for Clinician 1

Name: Amritanshu Shekhar Pandey

Position: Clinical adjunct professor, McMaster University, staff cardiologist (Cambridge Cardiac Rehab, Cambridge Memorial Hospital, and St. Mary's General Hospital)

Date: <25.06, 2023>

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Amgen	x			
HLS Pharmaceuticals	x			
Novartis	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Eileen Jang

Position: Nurse Practitioner (Cambridge Cardiac Rehab, Cambridge Cardiac Care Centre)

Date: <25.06, 2023>

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: <Dr. Andrea Rowe>

Position: Staff Physician, Cambridge Memorial Hospital and Cambridge Cardiac Care Centre

Date: <DD-MM-YYYY>

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: <Laura Kuehl>

Position: <RN>

Date: Nurse (Cambridge Cardiac Rehab, Cambridge Cardiac Care Centre

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				

Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: <Christopher Lo>

Position: < Nurse Practitioner (Cambridge Cardiac Rehab, Cambridge Cardiac Care Centre >

Date: <27.06.2023>

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: <Claudia Surd>

Position: < Nurse (Cambridge Cardiac Rehab, Cambridge Cardiac Care Centre >

Date: <27.06.2023>

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 6: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Clinician Group Input

CADTH Project Number: SR0791-000

Generic Drug Name (Brand Name): inclisiran (Leqvio)

Indication: LDL-cholesterol reduction

Name of Clinician Group: Canadian Cardiovascular Society Dyslipidemia Guideline Committee

Author of Submission: Ruth McPherson (with edits from clinicians listed below)

1. About Your Clinician Group

The Canadian Cardiovascular Society (CCS) dyslipidemia guidelines have been updated on a regular basis, most recently in 2021, to reflect new clinical trial and epidemiologic evidence (PMID: 33781847).

2. Information Gathering

The primary panel posed a number of population, intervention, comparator, and outcomes (PICO) questions to develop recommendations and inform clinical practice on the basis of a detailed literature review. The PICO format is a common standard used for guidelines development, to aid clinicians in determining whether the recommendations apply to their own patients with outcomes relevant to their practice. Initially, 13 different PICO questions were posed and then rated on the basis of the availability and significance of new evidence and importance to be included in the updated guidelines.

Using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) standards, individual studies and composite literature were reviewed for each PICO question with regard to the quality of the available evidence and the presence of publication or interpretive bias. For recommendations to go forward a two-thirds voting majority was required. Individuals with conflicts of interest were recused from voting on relevant recommendations.

Here PICO 4 is relevant to inclisiran.

3. Current Treatments and Treatment Goals

Health behavior modifications remain the cornerstone of chronic disease prevention, including CVD. In addition to smoking cessation and physical exercise, these include a reduction in dietary saturated fat and cholesterol to lower LDL-cholesterol, a reduction in sugar and other refined carbohydrates to reduce abdominal obesity and its associated risk factors, including triglyceride-rich lipoproteins and diabetes.

Studies consistently demonstrate a 20-22% ASCVD relative risk reduction for each 1 mmol/L reduction in low-density lipoprotein cholesterol (LDL-C). This benefit is independent of the specific dietary or pharmacological intervention.

Statins are recommended as the initial pharmacological agent to reduce ASCVD events, based on efficacy, safety, and cost. Ezetimibe is a useful second agent for individuals not achieving adequate control on a maximally tolerated statin dose. Large randomized controlled trials (RCTs) demonstrate that statins significantly reduce ASCVD events and total mortality, proportional to the achieved LDL-C.

A subset of high-risk individuals does not achieve adequate LDL-C control on statin/ezetimibe therapy and continue to experience myocardial infarction, stroke, heart failure and death.

PCSK9 targeted therapies are an appropriate *third line* approach for patients requiring additional LDL-lowering. The first PCSK9 inhibitors (evolocumab and alirocumab) are monoclonal antibodies that reduce LDL-C by 50 to 60% and in large RCTs, have been shown to reduce ASCVD events.

Relevant to the above section, the CCS panel addressed PICO 4.

PICO 4: In secondary prevention, what is the most appropriate lipid/lipoprotein threshold for the intensification of therapy?

1. We recommend use of high-intensity statin therapy in addition to appropriate health behaviour modifications for all secondary prevention CVD patients. For patients who do not tolerate a high-intensity statin, we recommend the maximally tolerated statin dose (Strong Recommendation; High-Quality Evidence).

2. We recommend intensification of lipid-lowering therapy with a PCSK9 inhibitor (evolocumab or alirocumab) – with or without the addition of ezetimibe – for secondary CV prevention patients shown to derive the largest benefit from PSCK9 inhibitor therapy in whom LDL-C remains ≥ 1.8 mmol/L (or non-HDL-C ≥ 2.4 mmol/L or ApoB ≥ 0.7 g/L) on maximally tolerated statin dose. (Strong Recommendation; Moderate-Quality Evidence).

Clinical trials have demonstrated that PCSK9 inhibitors are effective at lowering LDL-C in patients with heterozygous FH and in certain patients with homozygous FH (*note that ASCVD outcome trials have not been performed for patients with FH for ethical reasons).*

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

PCSK9 therapies have been an important addition to our therapeutic armamentarium, specifically for two groups of patients:

- Severe familial hypercholesterolemia with untreated LDL-C often 4 times normal
- High-risk ASCVD patients requiring achievement of very low levels of LDL-C to avoid recurrent events and death.

Evolocumab and alirocumab are excellent agents but use is limited by cost and coverage.

For patients without insurance, available support programs are limited, resulting in out-of-pocket costs ~ $300/month.

Many patients have very partial drug coverage with a yearly cap.

Even for those with private insurance plans, coverage for evolocumab and alirocumab remains limited.

Given the technology required for monoclonal antibody production, a very marked reduction in future cost is unlikely, even with future approval of biosimilars.

Evolocumab and alirocumab require self-injection, generally every 2 weeks, with disposal of 26 cartridges per year.

Although both evolocumab and alirocumab are stable if kept at room temperature for 30 days, the need for refrigeration at 3 to 4ºC for longer periods of storage is somewhat restrictive.

A subset of patients are needle aversive and decline to initiate or comply with self injection over time.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Inclisiran is an *alternative to evolocumab or alirocumab for patients requiring additional LDL-C lowering*.

Inclisiran targets the PCSK9 pathway, as do evolocumab and alirocumab, agents shown to reduce ASCVD events.

The molecular mechanism differs in that inclisiran is a siRNA that leads to the degradation of the mRNA encoding PCSK9 and relevant to safety, does so specifically in the cytoplasm of hepatocytes.

It has the advantage of subcutaneous injection every 6 months rather than every 2 weeks.

Inclisiran lowers LDL-C by approximately 50% versus 50 to 60% for the other PCSK9 therapies.

ASCVD outcome studies are underway but inclisiran can be expected to reduce ASCVD events to the extent that LDL-C reduction is achieved.

As noted above, inclisiran is a *third line therapy* for patients already on a maximally tolerated statin/ezetimibe regimen. (An exception applies to the rare very individuals with a *genetically determined myopathy or with a history of statin-induced rhabdomyolysis for whom statin therapy is an absolute contraindication).*

As an alternative third line therapy for patients who decline self-injection every 2 weeks, inclisiran can be expected to increase the number of high-risk patients in Canada who achieve the LDL-C levels associated with the lowest risk for ASCVD events.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

As stated in the 2021, CCS Dyslipidemia guidelines (PMID: 33781847), we recommend intensification of lipid-lowering therapy with a PCSK9 inhibitor– with or without the addition of ezetimibe – for secondary CV prevention patients shown to derive the largest benefit from PSCK9 inhibitor therapy in whom LDL-C remains ≥ 1.8 mmol/L (or non-HDL-C ≥ 2.4 mmol/L or ApoB ≥ 0.7 g/L) on maximally tolerated statin dose.

As stated in 2018 CCS Familial Hypercholesterolemia guidelines (PMID: 30527143), for patients with FH who do not have a clinical diagnosis of ASCVD, we recommend addition of a PCSK9 inhibitor to a high dose statin/ezetimibe for whom LDL-C remains ≥ 2.5 mmol/L. The diagnosis of FH must be made according to the Canadian FH guidelines. Genetic diagnosis is not a requirement.

For the above groups of individuals, inclisiran is a convenient alternative to evolocumab and alirocumab with established safety and efficacy in 3660 primary and secondary prevention patients (PMID: 37252442, PMID: 36839644).

Inclisiran is not a first line treatment. It is not recommended for primary prevention in patients without a diagnosis of FH or for secondary prevention in patients achieving adequate control on a statin/ezetimibe regimen.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

The outcome measured in clinical practice is the % reduction in LDL-C, 6 to 12 mos after initiating treatment with inclisiran. The median response expected based on clinical trial data is a 50% reduction in LDL-C (PMID 37252442). A clinically meaningful response is a >20% reduction in LDL-C.

It is not clinically feasible to access the effects of inclisiran on ASCVD symptomatology. Of note, in the COURAGE study, multi-modal risk factor intervention including intensive LDL-C lowering resulted in a 72% decrease in anginal symptoms at 5 years, similar to that achieved for patients treated with percutaneous intervention (PMID:17387127).

Ongoing clinical trials will determine the long-term morbidity and mortality benefits of inclisiran treatment.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

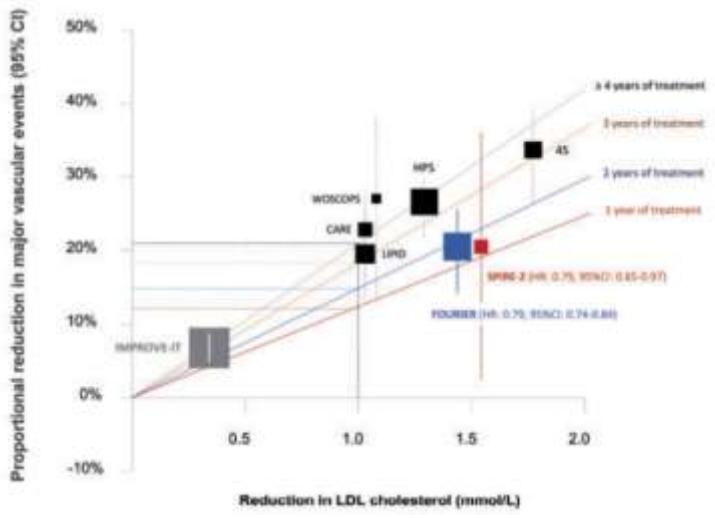
Continued treatment with inclisiran would not be appropriate for patients with life limiting (e.g. terminal malignancies) or quality of life limiting (e.g. severe dementia) conditions.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Inclisiran treatment can be initiated by a primary care physician (PCP) or any medical or surgical specialist with close attention to the above criteria. It can be administered by a nurse, physician, or pharmacist. Optimally, injections might accord with a q 6-month PCP visit to monitor LDL-C response, tolerability and to assure adherence.

6. Additional Information

While we await with interest the current ongoing ASCVD outcome trials with inclisiran, the committee believes that, based on 40 years of clinical trial data for statins and PCSK9i, LDL-C reduction is a viable surrogate for expected benefits and such benefits accrue over time (PMID: 29020411).



Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No external assistance was provided to complete this submission.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   None other than assistance from the CCS in preparing the 2021 CCS Dyslipidemia Guidelines

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

   The CCS Dyslipidemia Guideline committee was not provided with financial assistance from Novartis or any other pharmaceutical corporation.

Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.

Declaration for Clinician 1

Name: <G B John Mancini>

Position: <Professor of Medicine, UBC; Scientific Director, CardioRisk Clinic>

Date: <05-07-2023>

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis (Grants, Honoraria)				x

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Jean Gregoire

Position: Interventional Cardiologist, Montreal Heart Institute, Associate Professor, Université de Montréal,

Date: 05-07-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	**Check appropriate dollar range***

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Novartis			X	
HLS Therapeutics			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Todd Anderson, MD

Position: Dean, Cumming School of Medicine, University of Calgary

Date: July 05, 2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis			X	
Add company name				
Add or remove rows as required				

I am the local PI for the Victorian study. Novartis provides funding to the PCI research group in Calgary to pay nursing time to run the study. I do not receive any compensation for this role. I do not sit on any advisory boards or do talks for industry. This is the only study I am currently involved with. I am also a past co-chair and then member of the CCS dyslipidemia guidelines group.

Declaration for Clinician 4

Name: <Patrick Couture>

Position: <Professor of medicine, Department of medicine, Université Laval>

Date: <05-07-2023>

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis (Grants, Honoraria)		X		
Valbiotis (Grants, Honoraria)				X

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: David C W Lau

Position: Professor Emeritus of Medicine, Univ. of Calgary

Date: 05-07-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	X			
HLS Therapeutics	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Jacques Genest MD

Position: Professor of Medicine, Cardiologist, McGill University

Date: 06 July 2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 6: Conflict of Interest Declaration for Clinician 6

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: Eva M. Lonn

Position: Professor of Medicine, McMaster University; Medical Director, Cardiac Health and Rehabilitation Service, Hamilton Health Sciences

Date: 06-07-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 7: Conflict of Interest Declaration for Clinician 7

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Amgen	X			
HLS Therapeutics	X			
Novartis		x		
Nono Nordisk	X			
LIB Therapeutics	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 8

Name: Alexander Leung

Position: Associate Professor, Cumming School of Medicine, University of Calgary

Date: July 06, 2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 8: Conflict of Interest Declaration for Clinician 8

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
N/A				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 9

Name: Gordon Francis MD FRCPC

Position: Professor of Medicine

Date: 06-07-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 9: Conflict of Interest Declaration for Clinician 9

Company	**Check appropriate dollar range***

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 10

Name: Robert A. Hegele MD

Position: Staff Physician, London Health Sciences Centre

Date: <07-07-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 10: Conflict of Interest Declaration for Clinician 10

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Acasti	X			
Aegerion	X			
Akcea/Ionis	X			
Pfizer	X			
Regeneron	X			
Sanofi	X			
HLS Therapeutics		X		
Novartis			X	
Amgen			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 11

Name: George Thanassoulis

Position: Professor of Medicine, McGill University

Date: 07-07-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 11: Conflict of Interest Declaration for Clinician 11

Company	Check appropriate dollar range*

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Novartis			x	
Amgen			x	
Sanofi		x		
HLS Therapeutics		x		
New Amsterdam	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 12

Name: Nicholas Giacomantonio

Position: Director Cardiovascular Prevention and Management, Nova Scotia

Date: 11/07/2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 12: Conflict of Interest Declaration for Clinician 12

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis			X	
AMGEN			X	
HLS-Therapeutic's			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 13

Name: Daniel Ngui

Position: Clinical Professor, UBC Dept of Family Medicine, Medical Director Fraser Street Medical

Date: 11/07/2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 13: Conflict of Interest Declaration for Clinician 13

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**

Amgen	X			
Astra Zeneca	X			
Valeo	X			
Novo-Nordisk		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 14

Name: Ruth McPherson

Position: Professor of Medicine, Division of Cardiology, University of Ottawa Heart Institute

Date: 12/07/2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 14: Conflict of Interest Declaration for Clinician 14

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Amgen (Grants, Honoraria)			X	
Novartis (Grants, Honoraria)			X	
Pendopharm (Honoraria)	X			

* Place an X in the appropriate dollar range cells for each company.

Clinician Group Input

CADTH Project Number: SR0791-000

Generic Drug Name (Brand Name): Inclisiran

Indication: Hypercholesterolemia

Name of Clinician Group: Cardiology Associates of Niagara

Author of Submission: Adnan Kazi Hameed

1. About Your Clinician Group

The Cardiology Associates of Niagara (CAN) is a growing group of Cardiologists practicing in Niagara with hospital privileges. We care for patients with ASCVD in the hospital setting as well as in a community clinic. Our group meets monthly to discuss the latest research trials and our quality improvement and educational projects. We share best practices and discuss cases amongst ourselves and our other specialty colleagues. We aim to improve the care provided to cardiac patients in our region.

2. Information Gathering

Review of relevant research trials and Canadian guidelines coupled with experience in the field of cardiology.

3. Current Treatments and Treatment Goals

The established treatments at present include statins, ezetimibe and PCSK9 inhibitors coupled with dietary therapy to reduced unhealthy saturated fat intake. These therapies are regularly used and endorsed in the latest iteration of the Canadian lipid guidelines. Other medications such as fibrates and bile resins are seldom used due to poor tolerance and efficacy.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Not all patients achieve the guideline recommendations and the most recent iteration of these guidelines (2021) established new LDL-C thresholds lower than before. In addition, European guidelines are aiming for even more aggressive LDL reduction. Despite this knowledge the practical reality is that traditional therapies using statins and ezetimibe do not achieve desired results and are not well tolerated due to real or perceived side effects. Treatments are needed that can alter disease trajectory and improve adherence. The drug under review offers an advantageous dosing regimen which would improve adherence.

In addition, accessibility challenges circumvent widespread implementation of newer lipid lowering agents (PCSK9 monoclonal antibodies) due to high cost and lack of coverage for ASCVD indication on the provincial drug formulary.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

As an siRNA therapy targeting PCSK9, the drug under review improves lipid profiles (LDL-C, ApoB and non-HDL-C) by inhibiting PCSK9 production resulting in increased expression of hepatic LDL receptors. This mechanism, common to other lipid lowering therapies with proven effect on lowering CV risk would reduce LDL in patients with refractory lipid profiles. Previous studies have demonstrated that a 1 mmol reduction in LDL offers upto a 20% reduction in cardiovascular events.

The drug under review would be used as an add on therapy to maximally tolerated dose of statin with or without additional lipid lowering agents (ezetimibe) in patients who require additional further lipid lowering.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Patients on maximally tolerated doses of statin and ezetimibe with persistent LDL elevation above threshold would benefit from treatment. Additionally, patients with ASCVD with other markers of high risk, including: recent MI, CABG, multivessel disease, polyvascular disease, diabetes and elevated Lp(a). In addition, those patients who become refractory to statins and ezetimibe along with those who struggle with compliance would be best suited for the drug under review. Lastly, a number of high risk patients can not tolerate high dose statin therapy due to side effects and would benefit from the drug under review.

Conversely, patients with optimal lipid profiles on other lipid therapies or those with low cardiovascular risk would not be the target population for the drug under review.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

LDL-C, non-HDL-c and ApoB measurements align with the typical clinical practice and are endorsed by the Canadian lipid guidelines and broadly available for use.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Lack of response, intolerability or access to another therapy.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Specialty clinic, community outpatient clinic or hospital.

6. Additional Information

None.

7.

Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

   See below.

Declaration for Clinician 1

Name: Adnan Kazi Hameed

Position: Assistant Professor McMaster University, Head of Service Niagara Health System, Cardiology Associates of Niagara.

Date: 5/7/2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis				x
Amgen		X		
HLS Therapeutics		X		
Sanofi	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Marian Kotrec

Position: Cardiologist, Niagara Health, Cardiology Associates of Niagara; Adjunct Assistant Professor, McMaster University

Date: 5/7/2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	**Check appropriate dollar range***

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Novartis				x
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Alexandra Bojcevski

Position: Cardiologist, Niagara Health, Cardiology Associates of Niagara; Adjunct Professor, McMaster University

Date: 11/7/2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis				x
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Clinician Group Input

CADTH Project Number: SR0791-000

Generic Drug Name (Brand Name): Inclisiran (Leqvio)

Indication: Primary hypercholesterolemia

Name of Clinician Group: Service of cardiology, CHU Dr-Georges-L-Dumont

Author of Submission: Dr Luc Cormier

1. About Your Clinician Group

We are a group of 6 clinical cardiologist working at the CHU Dr-Georges-L.-Dumont, Moncton (NB). We share a cardiology clinic outside the hospital. All our clinical tasks are equally shared. We have multiple specialized clinics in cardiology, including a lipid clinic (provincial wide referrals). We have academic activities at multiple levels including pre-clinical medical students (medical school in Moncton), residents. We also are actively participating in clinical trials, and our group all share responsibilities in this regard.

2. Information Gathering

- Published data on inclisiran

- Current data on lipid management.

- Guideline based therapies and recommendations.

3. Current Treatments and Treatment Goals

Current treatment on dyslipidemia have shown clear correlation between LDL reduction and CV outcome reduction. This data has been consistent in the Cholesterol Treatment Trialists data, and this includes statins, ezetimibe, and PCSK-9 inhibitors. Current treatments have a very good efficacy in CV risk reduction, namely risk of CV death, risk of MI, risk of stroke, risk of limb amputation which are the most hard and compelling data.

It remains clear that there have been two main mechanisms of LDL-C management that have shown very significant effects in LDL reduction:

1. HMG-coA-reductase upregulation to increase LDL receptor production in hepatocytes; statins can achieve LDL reduction by as much as 55-65% in high potency statins;

2. PCSK-9 downregulation: both monoclonal anti-bodies (PCSK-9 inhibitors) have shown reduction of LDL-C by about 50-60%, and siRNA (inclisiran) by about 50% reduction of LDL-C

All other mechanisms mainly through absorption of LDL (includes diet) either with ezetimibe and bile-acid sequestrants only reduce LDL by about 15% on average. As such, in order to gain meaningful cardiovascular protection, large reductions of LDL-C are warranted. This large reduction of LDL-C has been associated with reduced CV risk in two large studies with PCSK-9 inhibitors, as intensification therapy over statins. The results of the FOURIER and ODYSSEY-OUTCOMES trials have shown largely similar results in terms of CV risk reduction:

Table 1: CV protection related to PCSK-9 inhibitors

Trial	Medication tested	Results
FOURIER trial	Evelocumab (Repatha)	Evelocumab add-on to statin reduced CV event is people with ASCVD Primary Endpoint: CV Death, MI, Stroke, Hospitalization for Unstable Angina or Coronary Revascularization; HR 0,85 (95% CI, 0,79 – 0,92) p<0,001)

		Secondary Endpoint: CV Death, MI or Stroke; NNT 67 over 2.2 years primary endpoint.
Reference : Sabatine MS et al. *N Engl J* Med 2017;376:1713–22		
ODYSSEY-OUTCOMES	Alirocumab (Praluent)	Alirocumab Add-on to Statin Reduced CV Events in People with ACS (within 1 to 12 months) Primary Endpoint**:** Time to first occurrence of CHD death, non-fatal MI, ischemic stroke, or UA requiring hospitalization; NNT 63 over 2.8 years; HR 0.85, (95% CI, 0.78-0.93) p<0.001
Reference : Schwartz GG et al. *N Engl J Med*. 2018;379:2097-2107		

Again, this data when plotted on the Cholesterol Treatment Trialists (CTT) regression line, we can appreciate in Figure 1 of Ference et al.[92], the effect of treatment compared to other LDL-C reduction therapies including non-statins (ezetimibe). Figure 1 (a) of Ference et al.[92] represents total effect of different treatments on CV risk reduction, whereas Figure 1 (b) of Ference et al.[92] shows the effect as per duration of treatment in the various trials.

These points strongly demonstrate that the LDL-C hypothesis has been shown to be considered established well enough and most guidelines suggest that lower LDL with drugs that have more significant potency are strongly associated with CV risk reduction.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Unfortunately, there remains a large need in lipid management to reduce LDL-C to meaningful levels in order to reduce CV risk. As such, either because of true or perceived statin tolerance, or insufficient effect, as much as 40% of Canadians do not have lipids managed at the desired level as per Canadian guidelines. This was demonstrated in a Canadian population in DYSIS (45% had LDL-C > 2,0). There is also contemporary Canadian data showing that after an MI, only about 45% of patients on high intensity statin and ezetimibe have an LDL-C below 1,8 (figure 3A of Mackinnon et al.[8]).

Whereas, the Canadian setting currently have two PCSK-9 inhibitors currently available on the market for use, the penetrance of these agents are severely limited due to insurance coverage, costs, administrative barriers for coverage, these agents are severely restricted in the current Canadian setting. Our group estimates to less than 5% (very conservative number, likely less) of our eligible patients for PCKS-9 inhibitors are not on these treatments for above mentioned reasons. Furthermore, we have a clinic with good clerical support, nursing support for difficult to treat patients or high risk or hereditary dyslipidemias, and coverage with PCKS-9 inhibitors remain a challenge despite this.

Furthermore, extrapolating data from the recent publication from Mackinnon et al. which showed an incidence of ASCVD of 75,5 cases per 1000 people in Ontario between 2008 and 2017, this could roughly suggest that there are about 3 million Canadians suffering from ASCVD in this reference time. As a group, we have heard that there have been about 12,000 prescriptions of PCSK-9 inhibitors in Canada in the past 7 years. We cannot reference this, and are uncertain how to check the veracity of this claim, but if this represents an approximation of reality in the canadian landscape, this suggests that much less than 1% of Canadian were treated with PCSK9-inhibitors over the past 7 years. We cannot believe that PCSK-9 inhibitors have been able to bridge the unmet need, based on very coarse numbers.

Furthermore, compliance to injectable medication can also be considered, as to the persistence of treatments. Injections of PCSK-9 inhibitors every 2 weeks versus injection with inclisiran every 6 months by a healthcare professional will likely greatly improve compliance with the 6 months period.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

The role of inclisiran would essentially become an intensification therapy for patients who are not at desired target level of LDL-C despite maximal tolerated dose of statin, who are considered at high risk of CV event: ASCVD patient, primary prevention with high

risk (many definitions could be applied, could be considered as per Canadian dyslipidemia guidelines) as well as familial hypercholesterolemia patients.

Inclisiran has a potent LDL-C reduction capability such as demonstrated by the pooled published data from ORION-9, -10 and -11 trials (Figure 2 A of Wright et al.[91])

The same data was also examined as to whether there is a sign that it is associated with CV risk reduction. The ORION-9-10-11 trials were designed to assess LDL-C reduction, safety, and collected data from adverse event which includes CV event were plotted on a Kaplan-Meyer graph. This data (not adjudicated) is not definitive but certainly uphold the LDL-C hypothesis with treatment of Inclisiran (Figure 2A of Ray et al.[81]).

We are not acknowledging that inclisiran have the same CV protection as an intensification treatment, equivalent to PCSK-9 inhibitors, especially for the ASCVD. However, some patients do not have access to PCSK-9 inhibitors for various reasons mentioned previously, or do not want to self-administer PCSK-9 inhibitors every 2 weeks, but would accept injection every 6 months by a healthcare professional.

As such, despite having a LARGE unmet need for therapy intensification beyond high potency statins, PCSK-9 inhibitors have not been able to address the large gap in therapy goals across the country, and as such, no meaningful populational gains were provided in CV risk reduction with the introduction of PCSK-9 inhibitors in Canada. After maximally tolerated statin therapy and LDL-C remains elevated, there is no standard of care for treatment intensification in Canada, and PCSK-9 inhibitors are not standard of care by any measure, since they are not the standard in a real clinical setting, since we cannot get reasonable access.

This review, if positive, could push access inclisiran to significant price lowering, with the goal to have less “special access control” (which ends up being “restrictive” access, such as the current state of use of PCSK-9 inhibitors in clinical practice). This review would be an opportunity to suggest wider access to the drug with very aggressive price lowering might give us tool to better bridge the gap.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

As mentioned above, the patients best suited for this medication are any patient with indication for LDL lowering indication (CCS dyslipidemia guidelines) who are above threshold for intervention while on maximally tolerated dose of statin. Examples of patients that will likely gain most absolute risk benefit are patients with:

- ASCVD especially with enhanced risk features such as polyvascular disease, diabetes, CKD, recurrent events.

- Familial hypercholesterolemia

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

As for lipid management, the measured primary outcome is CV events (death, MI stroke). However, there is consistent and good correlation of LDL-C reduction and CV risk reduction as previously mentioned, and this is true with all agents that reduce LDL-C as per the CTC analyses.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

No specific adverse events are reported.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

This medication should be accessible to primary care provider as per intensification of treatment for LDL-C.

6. Additional Information

Conflict of Interest Declarations

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2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr Luc Cormier

Position: Clinical cardiologist, clinical lead for the lipid clinic

Date: 2023-07-12

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

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Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis		X		
Amgen		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr Michel D'Astous

Position: Clinical cardiologist

Date: 2023-07-12

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	**Check appropriate dollar range***

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Novartis	X			
Add company name				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr Jean-François Baril

Position: Chief of cardiology, clinical cardiologist

Date: 2023-07-12

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Dr Rina Lee

Position: Clinical cardiologist

Date: 2023-07-12

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr Stéphanie Thébeau

Position: Clinical cardiologist

Date: 2023-07-12

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Dr Annaelle Kaczmarek

Position: Clinical cardiologist

Date: 2023-07-12

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 6: Conflict of Interest Declaration for Clinician 6

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				

* Place an X in the appropriate dollar range cells for each company.

Clinician Group Input

CADTH Project Number: SR0791-000

Generic Drug Name (Brand Name): Levqio

Indication: Inclisiran is indicated in adults with primary hypercholesterolemia (FH and nonfamiliar FH) in conjunction to diet. In patients on maximum tolerated dose of statin, with or without the use of Ezetimide, that have not achieved target LDL C levels.

Name of Clinician Group: Egyptian Cardiologists of Niagara

Author of Submission: Rosemonde Tannous, MB, BSc, ABIM, Cardiology

1. About Your Clinician Group

Two experienced community cardiologists that cover the South Niagara Region with subclinical interests in clinical epidemiology, supported by a clinical pharmacist working in an intensive care unit and is a diabetic educator.

2. Information Gathering

With 62 years of combined clinical experience and supported by review of the most up to date relevant literature and clinical publication, we were able to gather this information.

3. Current Treatments and Treatment Goals

Current Canadian lipid guidelines (2021) and CCS guidelines endorse the use of a statin to maximum tolerated dose to achieve target LDL levels along with diet and weight reduction, with or without the addition of Ezetimide and PCSK9 inhibitor. We are aware that, for every reduction of LDL by 1mmol/L, the literature shows a 20% reduction in major vascular and coronary events in over 90,000 patients in 14 statin trials. Despite this, a large proportion of patients on current therapy has not reached target LDL levels.

As mentioned above in the meta-analysis, the reduction of LDL to target levels achieves the ultimate goal of any new lipid lowering drug. This will also translate to a reduction in cardiovascular events.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Current treatments fail to achieve target LDL levels in 30% of patients, and some patients are intolerant to statins and therefore unable to use them. In conjunction with LDL reduction, an ideal drug would also reduce non-HDL C, Apo B, and if possible, Lpa. An ideal treatment would be easy to use for both patients and clinicians, well-tolerated by patients with the fewest side-effects, and therefore maximize patient compliance. The treatment should have the best safety profile. Only a small proportion of patients are able to access innovative add-on injectable lipid-lowering therapies due to lack of insurance coverage. Statins have known side-effects which cause low compliance. Agents which are easy to use and well-tolerated are very much needed.

Inclisiran, being subcutaneous injection every 6 months, would significantly improve patient compliance, especially those on polypharma. If access to this new therapy is provided to a wider population, overall cardiovascular outcomes will improve.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

While statins reduce LDL C by inhibiting HMG Coa reductase, the SiRNA PCSK9 inhibitor would increase LDL receptors on the hepatocyte cell surface and hence reduce LDL C by a different but complimentary mechanism of action. The expression of LDL C receptors is increased by the inhibition of PCSK9 protein production intracellularly by interference of mRNA translation. What this means clinically is significant LDL C reduction in addition to maximum standard therapy that is safe and well-tolerated. Inclisiran is the first in class for SiRNA PCSK9 inhibitor.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

ASCVD patients with high-risk disease, including coronary artery disease, cerebrovascular disease, peripheral arterial disease, and polyvascular disease, would most benefit from this therapy, along with diabetics with high risk factors or comorbidities such as CKD. Additionally, patients who are elderly or younger patients without private insurance would benefit from this therapy if access is expanded. All of these patients are reflective of my practice patient population.

Patients that are least suited to this new therapy are those that have no indication of the use of a statin and those that have already achieved target LDL C levels, in addition to patients that will not attempt the use of even a small dose of statin once indicated by their physician.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

As per the 2021 CCS Lipid Guidelines, a reduction in all lipid panel parameters including LD, non-HDL C, and Apo B Lpa, would result in reduction of clinical endpoints. A meaningful response to treatment would translate into a reduction of cardiovascular events and decreased mortality. Treatment response should be assessed by obtaining a repeat lipid profile on the patient after the first 6 months of therapy and yearly thereafter. With this 6-monthly injection schedule, the physician will be able to follow the patient holistically.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Only patient choice would be considered for discontinuation of this drug, given the very low probability for major side effects. The drug is safe and well-tolerated.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

A specialist is required to diagnose the patient condition indicating need for this drug, particularly cardiologist, endocrinologist, Diabetes clinicians, general internist, and lipid specialists. This can be facilitated in either the specialist's office, family practice office, hospital medical clinic, or community outpatient clinic settings.

6. Additional Information

No.

Conflict of Interest Declarations

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3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Rosemonde Tannous

Position: Community Cardiologist

Date: 08-07-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

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Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Alfi Moris Beshay

Position: Internal Medicine, Cardiovascular Disease Consultant & Clinical Lipidologist.

Date: 13-07-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	**Check appropriate dollar range***

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Mona Ebeid

Position: Clinical Pharmacist, Diabetes Educator at Niagara Health

Date: 12-07-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

* Place an X in the appropriate dollar range cells for each company.

Clinician Group Input

MICHAEL C. HARTLEIB, MD, FRCPC

CARDIOLOGIST

Michael C. Hartleib Medicine Professional Corporation

THE KAWARTHA CARDIOLOGY CLINIC [redacted]

327 Charlotte Street [redacted]

Peterborough, Ontario

K9J 0B2

To Whom It May Concern:

RE CADTH Inclisirin Reimbusement Review

CADTH Project number: SR0791-000
Generic Drug Name: Inclisiran
Indication: LDL Lowering
Name of Clinician Group: Kawartha Cardiology Clinic
Author of Submission: Dr. Michael C Hartleib

1. About Your Clinician Group

The Kawartha Cardiology Clinic provides care to patients in Peterborough and the entire north-east cluster of the Central East LHIN in Ontario. Currently there are 7 cardiologists working at the clinic. This document reflects the collected responses and opinions of the physicians identified herein. www.kawarthacardiology.com

3. Current Treatments and Treatment Goals

LDL lowering remains the cornerstone of risk reduction for patients with vascular disease. We have efficacious therapies (eg statins, ezetimibe, evolocumab, alirocumab) that are broadly used in Canada. Current guidelines recommend that high-risk patients should receive additional aggressive therapy for and LDL>1.8.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Despite currently available therapies, due to intolerance or non-adherance up to 50% of high-risk patients in Canada are not able to achieve currently identified treatment targets, which leaves them at substantially increased risk for recurrent events.[2,3] It should be noted that many jurisdictions have treatment targets that are substantially more aggressive than Canadian targets.[4] There is an acute need for an agent that successfully lowers LDL, is well tolerated, and geared to optimization of adherence.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

It has been established that LDL-C lowering, primarily although not exclusively, via upregulation of LDL receptor expression leads to substantial risk reduction This has been demonstrated in several non-statin based pharmacologic approaches such as ezetimibe,

PCSK9 inhibitors, as well as non-pharmacologic mechanisms such as ileal bypass.[1,2] Therapies that have demonstrated efficacy in special patient populations (eg PCSK9 and FH) have been approved despite a paucity of outcomes data. While the longer term outcome studies assessing inclisiran are ongoing, retrospective review of patient level data from early trials have demonstrated a reduction in vascular events consistent with the LDL hypothesis.[5] Accordingly, the demonstrated safety and efficacy of inclisiran in sustained lowering of LDL, associated with a risk reduction that is consistent with the LDL hypothesis is, in our opinion, sufficient to warrant availability of another important option for high-risk patients who are not able to meet treatment targets with currently available therapy.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

The focus of therapy should be risk reduction in the highest risk patients eg those with recurrent events or poly-vascular disease. These patients are well defined in current guidelines as those patients with an event within the last year, or patients with recurrent ACS, diabetes, symptomatic PAD and poly-vascular disease.[2]

As has been identified many patients are completely or partially intolerant of currently available lipid lowering strategies or struggle with adherance. Our clinical experience with inclisiran thus far has been uniformly positive with patient comments such as "***Finally, something I don't have to worry about, and I know I am protected***" and "***That's it?*** (post injection). ***That was nothing, to think all this time this is what I have been waiting for…thank you!".***

Having multiple therapies available will only increase the clinician's ability to optimally treat high risk patients with significant societal impact related to lowering of first events, recurrent events, as well as mortality. significant and sustained LDL-C lowering with both ease of use and which resolves concerns associated with adherence.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Patient outcomes can be assessed via monitoring of LDL levels as is done with currently available therapies.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Inclisiran is safe and well tolerated without the need for dose adjustments in patients with renal and hepatic disease (although has not been studied in patients with more advanced hepatic impairment (Child-Pugh C). Adverse reactions have been found to be similar to placebo in clinical trials. Injection site reactions are typically minor and resolve quickly. Accordingly, as inclisiran is broadly safe and well tolerated, consideration of discontinuation will need to be a shared decision made by clinicians and patients.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

No special setting should be required. Injections could be performed with primary care, specialists or in pharmacies.

While this document has been created based on our real-world clinical experience as well as our understanding of the current medical literature, we are also cognizant of other decision-making bodies such as the National Institutes of Clinical Excellence in the United Kingdom which has provisionally provided a positive review for the use of inclisiran. We hope to have the same access to optimal medical care for our patients.

With the above in mind, we formally request that the committee reconsider their decision such that this unique and necessary therapy can be made available to busy clinicians and high-risk patients.

6. Additional Information

Not at this time.

Conflict of Interest Declarations

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Michael C Hartleib

Position: Cardiologist

Date: 10 July 2023

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	x			
Amgen	x			

Declaration for Clinician 2

Name: Dr. William G Hughes

Position: Cardiologist

Date: 10 July 2023

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	x			

Amgen	x			

Declaration for Clinician 3

Name: Dr. Katie Doucet

Position: Cardiologist

Date: 10 July 2023

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	x			
Amgen	x			

Declaration for Clinician 4

Name: Dr. Karen Wagner

Position: Cardiologist

Date: 10 July 2023

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	x			
Amgen	x			

Declaration for Clinician 5

Name: Dr. John Reesor

Position: Cardiologist

Date: 10 July 2023

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

Declaration for Clinician 6

Name: Dr. Rachelle Krause

Position: Cardiologist

Date: 10 July 2023

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 6: Conflict of Interest Declaration for Clinician 6

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	x			

Declaration for Clinician 7

Name: Dr. Andrew Kelly

Position: Cardiologist

Date: 10 July 2023

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 7: Conflict of Interest Declaration for Clinician 7

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

1. Silverman et al., JAMA, 2016; 316(12): 1289-1297.
2. Pearson et al. CJC, 2021; 37: 1129-1150.
3. Bates et al, Expert Opin on Pharm, 2009; 10(18): 2973-2985.
4. *Mach et al., European Heart Journal*, 2020; 41(1): 111-188.
5. Ray et al., European Heart Journal, 2023; 44(2): 129-138.

Sincerely,

Michael C Hartleib, MD, MSc, FRCPC

Chief and Director of Medicine, Peterborough Regional Health Centre
Director, Kawartha Cardiology Clinical Trials
Peterborough Regional Health Centre
Kawartha Cardiology Clinic
327 Charlotte Street, Suite 204
Peterborough, Ontario, K9J 0B2
On Behalf of:

Dr. William Hughes

Dr. Katie Doucet

Dr. Karen Wagner

Dr. John Reesor

Dr. Rachelle Krause

Dr. Andrew Kelly

Clinician Group Input

CADTH Project Number: SR0791-000

Generic Drug Name (Brand Name): Inclisiran

Indication: Primary hypercholesterolemia

Name of Clinician Group: N/A

Author of Submission: Guillaume Pare

1. About Your Clinician Group

I am clinician specialized in lipidology working at the Lipid Clinic of McMaster University and Hamilton Health Sciences.

2. Information Gathering

Review of relevant literature and publications as well as background knowledge in the area.

3. Current Treatments and Treatment Goals

Treatment of primary hypercholesterolemia is currently based on statins (first line therapy), ezetimibe and PCSK9 monoclonal antibodies, in addition to dietary advice consisting of reducing saturated fat intake, increasing fiber intake and adapting a generally healthy and balanced diet. These recommendations are endorsed by the Canadian Cardiovascular Society dyslipidemia guidelines. Other medications include bile acid sequestrants and niacin but are seldom used due to poor tolerance and lack of evidence for CV risk reduction (niacin). Overarching treatment goal is to optimize CVD risk through reduction in LDLc / apoB / non-HDLc.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Unfortunately, many patients are unable to meet treatment goals. The main reasons are:

- Intolerance to currently available treatments, particularly statins
- Lack of compliance to treatment
- Variable response to currently available treatments
- Lack of accessibility (i.e. cost) to highly effective PCSK9 inhibitors.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Inclisiran would be used as adjunct therapy in individuals on maximally tolerated dose of statin and ezetimibe not meeting treatment targets. Inclisiran is a PCSK9 inhibitor, a class for which substantial evidence supports clinical benefit. Furthermore, inclisiran has been shown to be effective at decreasing LDLc / apoB / non-HDLc in this patient population.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

As stated above, Inclisiran would be used as adjunct therapy in individuals on maximally tolerated dose of statin and ezetimibe not meeting treatment targets. While other PCSK9 inhibitors (monoclonal antibodies) are available, as a siRNA inclisiran has the advantage of being administered only twice a year instead of bi-weekly / monthly. Furthermore, inclisiran can be stored at room temperature and does not need to be refrigerated like monoclonal antibodies. This would enable patients whose work requires frequent / extended travels, such as forest firefighters and many others, to benefit from PCSK9 inhibition therapy.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Treatment response is easy to assess with measurement of LDLc / apoB / non-HDLc pre- and post-treatment initiation.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Lipid lowering therapy seldom needs to be discontinued. Factors to consider: (1) substantial changes in lifestyle and diet with reduction in need for lipid lowering therapy, and (2) clinically significant local reactions at the injection site.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

A specialist is not needed. Treatment could be prescribed by family physicians, cardiologists, endocrinologists, stroke neurologists, vascular medicine specialists and lipidologists. Injection of inclisiran must be done by a HCP.

6. Additional Information

N/A

Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No

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   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

N/A

Declaration for Clinician 1

Name: Guillaume Pare

Position: Lipidologist, Hamilton Health Sciences. Professor of Pathology and Molecular Medicine, McMaster University

Date: 14-07-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Amgen	X			
Novartis	X			

* Place an X in the appropriate dollar range cells for each company.**CADTH Reimbursement Review Clinician Group Input**

CADTH Project Number: SR0791-000

Generic Drug Name (Brand Name): Inclisiran (Leqvio)

Indication: Primary hypercholesterolemia

Name of Clinician Group: Mazankowski Alberta Heart Institute

Author of Submission: Robert C. Welsh MD

1. About Your Clinician Group

At the Mazankowski Alberta Heart institute (MAHI), we focus on cutting edge secondary preventative therapies in patients with established atherosclerotic cardiovascular disease (ASCVD). We have robust secondary prevention clinics that focus on meeting all

guideline metrics for secondary prevention, including (but not limited to) robust reductions in LDL-C (known as a potent marker of atherogenic risk).

https://www.albertahealthservices.ca/maz/maz.aspx

2. Information Gathering

Review of current literature and current Canadian and international lipid guidelines as well as important randomized and observational studies pertaining to dyslipidemia and ASCVD. Reflection on background knowledge for ASVCD pertaining to interventional cardiology provided a background for further cited information.

3. Current Treatments and Treatment Goals

LDL-C lowering therapies approved by Health Canada include statins, ezetimibe, PCSK9 monoclonal antibodies and recently inclisiran (an siRNA targeting PCSK9 protein production), in conjunction with dietary and lifestyle modifications. Bile acid resins while available are not considered potent LDL-C lowering agents and are rarely used in practice. They are generally not well tolerated at maximum doses with limited evidence showing any advantage in reducing CV events. Lomitapide is another LDL lowering therapy that is limited to use in Homozygous Familial Hypercholesterolemia (HoFH) patients.

An ideal treatment would produce robust reductions in LDL cholesterol, non-HDL cholesterol and apolipoprotein B, have a favorable safety profile and be well tolerated. This would also translate to reducing the risk of major adverse cardiovascular events (MACE) and cardiovascular (CV) mortality. Given the challenges with adherence to current lipid lowering therapies, an ideal drug should be administered by a healthcare practitioner to ensure compliance and is ideal with this therapeutic agent given the infrequent dose administration.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Although optimal lipid control is guideline driven, access to potent add-on therapies to achieve guideline recommended targets, patients' nonadherence and drug intolerance are among the main barriers to achieving these targets. Pharmacotherapy with statins is still the cornerstone of dyslipidemia treatment; however, evidence from Canadian and international studies have shown that many Atherosclerotic Cardiovascular Disease (ASCVD) patients fail to achieve guideline-recommended LDL-C goals with statin monotherapy. In a retrospective study of ASCVD patients in Alberta, 48.5% of patients receiving any lipid lowering therapy (LLT) did not achieve the 2016 CCS guidelines recommended LDL-C levels (< 2 mmol/L or a > 50% reduction). A follow-up LDL-C measurement revealed that 36.6% of these patients continued to have suboptimal LDL-C levels within 1 year of an ASCVD diagnosis (Can J Cardiol. 2019;35:884) These numbers would be even higher today given the 2021 CCS guideline recommendations which now target a lower threshold of 1.8 mmol/L for treatment intensification in ASCVD patients. These results (along with those of other provinces) highlight the unmet need for novel add-on therapies in ASCVD management.

Limited access to PCSK9 inhibitors remains a challenge due to the high cost of these therapies and lack of coverage for certain ASCVD indications. This underscores the need for greater access to highly effective therapies, which in turn increase the number of patients achieving guideline defined treatment goals. Additionally, many patients' perceived side effects and intolerance to statins and ezetimibe is linked to adherence to these therapies. This highlights another treatment gap, which could be addressed by agents with improved tolerability and favorable dosing interval.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Inclisiran works by interfering with hepatic production of PCSK9, a protein responsible for altering LDL receptor recycling and facilitating its degradation. With less PCSK9 available, LDL receptors can be recycled back to the surface of hepatocytes, thereby reducing plasma LDL-C. Statins, which lower LDL-C levels by inhibiting HMG-CoA reductase (an enzyme essential for cholesterol production in the liver), have been shown to significantly increase plasma PCSK9 levels. Given the role of PCSK9 in regulation of LDL receptors, increases in PCSK9 concentration may limit the beneficial effects of statin. Inclisiran has a synergistic mechanism of action to statins, considering it significantly reduces intracellular and extracellular PCSK9 levels. Inclisiran is appropriate for use as an add-on therapy to maximally tolerated doses of statins and/or ezetimibe in patients who need additional therapies to achieve and maintain optimal lipid levels.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Through a robust clinical program, Inclisiran has been established as a well-tolerated and effective LDL-C lowering strategy. Any patients with or at risk of ASCVD who require additional lipid lowering therapy (LLT) would be a suitable candidate for inclisiran. Particularly, patients who would most benefit from inclisiran are those with established ASCVD who require add-on therapies for secondary prevention, and those with high risk of developing ASCVD (patients with HeFH, DM or high Framingham Risk Score). In Alberta alone, there are approximately 450,000 people living with ASCVD. Each year, 40,000 Albertans have a new ASCVD event. Following an initial ASCVD event, people are at a substantially increased risk of recurrent events that further impact their quality of life and increase the direct costs to the health care system, as well as indirect costs to society with loss of productivity. For example, based upon research utilizing Alberta population data sets , we have shown that in patients with a first MI, approximately 35% have a recurrent major adverse cardiac event and one quarter die within 5 years (PLoS One. 2021 Jul 1;16(7):e0254008).

In addition to those patients with a documented ASCVD event, there is a large number of at-risk people in our population with 9 out of 10 Canadian adults known to have at least one ASCVD risk factor. Patients with documented ASCVD (secondary prevention) and patients at highest risk of developing ASCVD combined are considered High Risk ASCVD patients. In Alberta, this is associated with a direct cost of greater than 1 billion dollars yearly based on Alberta Health data analysis (Pharmacoecon Open 2021;5:425). Extensive international and Canadian research efforts have provided effective interventions to reduce ASCVD risk. Interventions known to reduce further risk of events have the largest impact and is most cost effective when applied to patients with high-risk ASCVD. Although there are various interventions that are associated with improved outcomes, management of lipids is a central and key factor that has been extensively studied. Lifetime exposure to abnormal LDL cholesterol is a major driver of ASCVD. Despite this knowledge, only 10% of Albertans with High Risk ASCVD have appropriately controlled cholesterol risk. Alberta evidence shows that those with optimal control have a 43% lower risk of death over three years. When focusing on those with documented ASCVD (secondary prevention), optimal lipid management is associated with >3-fold reduction in 1 year mortality (1 year mortality of 0.7% compared to 3.1%). Further, this is achieved at cost neutrality for the health care system, saving on hospitalization costs.

Patients least suited for inclisiran would be those who have not attempted statin therapy of any dose. Inclisiran should not be used in patients with severe hepatic impairment as this patient population was excluded in the clinical trials, or those who are on dialysis or have an eGFR less than 15 mL/min.

Patient identification would be based on diagnostic criteria for FH or ASCVD and testing their lipid profile parameters including LDL-C, non-HDL-C and ApoB, which are widely available and used in contemporary clinical practice. Underdiagnosis of FH is a major problem in most countries. In Canada, it is estimated that only ~15% of FH patients have been identified, and often these patients are diagnosed later in life.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Outcomes measured in the clinical trials of inclisiran were changes in LDL-C, TC, non-HDL-C and ApoB. These outcomes are aligned with those used in the Canadian clinical practice, and the LDL-C threshold used is reflective of those recommended by the 2021 CCS guidelines.

A clinically meaningful response to treatment would be indicated by at least a 30% reduction in LDL-C or non-HDL-C levels. Treatment responses should be assessed every 3-6 months at the start of the treatment and less frequently (yearly) once the patient achieves optimal lipid levels while on a consistent treatment regimen.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Treatment discontinuation should be considered in patients lacking response to inclisiran (which is rare as per clinical trial data)

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Any in-hospital specialty clinic, community outpatient clinic, or pharmacy clinic are appropriate settings. In addition to specialists (cardiologists, internists, endocrinologists, etc), primary care physicians and pharmacists with prescribing authority should also be able to prescribe and administer inclisiran. In practice, many ASCVD patients are followed by specialists during the early months of treatment, which would be an ideal time to initiate lipid lowering therapy.

6. Additional Information

N/A

Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Robert C Welsh MD

Position: Professor of Medicine (Cardiology)

Date: 14-07-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis		X		
Bristol-Myers-Squibb	X			
Bayer		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Kevin R. Bainey MD, MSc

Position: Associate Professor of Medicine (Cardiology)

Date: 14-07-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	**Check appropriate dollar range***

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Novartis	X			
HLS therapeutics	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Paolo Raggi MD

Position: Professor of Medicine (Cardiology)

Date: 14-07-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	X			
Amgen	X			

* Place an X in the appropriate dollar range cells for each company.

Clinician Group Input

CADTH Project Number: **SR0791-000**

Generic Drug Name (Brand Name): **Inclisiran**

Indication: **Inclisiran is indicated 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, or**
- **Non-familial hypercholesterolemia with atherosclerotic cardiovascular disease**

Name of Clinician Group: **Oakville Cardiologists**

Author of Submission: **Dr. Michael Heffernan**

1. About Your Clinician Group

Oakville Cardiologists represents a large cardiology group practicing in Oakville, Ontario. We participate in the management of patients with cardiovascular disease in a region which encompasses a population of approximately 650,000 people. Our group of cardiologists meet regularly to share best practices and we collaborate on research and educational projects to improve the care of patients with cardiovascular disease in our community.

2. Information Gathering

Review of relevant literature and publications in addition to extensive background knowledge in this field.

3. Current Treatments and Treatment Goals

Dyslipidemia represents a significant health concern in Canada, with a substantial proportion of the population affected by this condition. According to recent epidemiological studies, approximately 40% of Canadian adults have dyslipidemia. The 2021 Canadian Dyslipidemia Guidelines recommend lifestyle modifications to improve lipid parameters while recognizing that only a modest reduction in LDL-C can be achieved in this manner. The vast majority of patients (both primary and secondary) require pharmacological therapy in order to achieve an LDL-C, non-HDL or Apo B below threshold. The guidelines recommend statins as the initial therapy for all high risk patients (≥ 20% 10-year risk) and intermediate risk patients (10-19.9%) when LDL-C is > 3.5 mmol/L (or apolipoprotein B > 1.05 g/L or non-high-density lipoprotein > 4.2 mmol/L) and for those with an LDL-C > 5 mmol/L. Studies consistently demonstrate a 20-22% relative risk reduction of cardiovascular events for each 1 mmol/L reduction in low-density lipoprotein cholesterol (LDL-C).

For those patients in which the lipid threshold cannot be achieved additional therapies are recommended in the 2021 Canadian Dyslipidemia Guidelines. These include ezetimibe and PCSK9 inhibitors.

Ideal pharmacological therapies in this field aim to lower the lipid parameters below the thresholds outlined in the 2021 Canadian Dyslipidemia Guidelines in order to reduce the incidence of major adverse cardiovascular events. These therapies should be efficacious and have a favourable safety profile.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

1.Tolerability.

This is a major clinical issue since many patients perceive side-effects when taking statins and/or ezetimibe. This leads to discontinuation of therapy and thereby a significant treatment gap. Sub-optimal therapy increases the risk for major adverse cardiac events. Efficacious therapies with lower rates of perceived side-effects are critical in this field of medicine to reduce the burden of disease.

2. Compliance.

Data has consistently shown that patients who adhere to their statin regimen experience a substantial reduction in the risk of heart attack, stroke, and other major cardiovascular events. Long-term compliance is associated with improved survival rates and a lower incidence of complications. Unfortunately, statin non-compliance is common and non-adherence increases the risk of adverse events. Therapies that allow for fewer dosing intervals and when also combined with medical supervision would be expected to improve long term compliance.

3. Treatment Goals.

Despite existing therapies, many patients do not achieve lipid values below their guideline-recommended thresholds. Add-on therapies are therefore needed to allow patients to reach their lipid targets. The current 2021 Canadian Dyslipidemia Guidelines have established thresholds that are lower than previous and as such many patients are not able to achieve the thresholds with the existing available and tolerated therapies.

4. Accessibility.

The high cost of mAb PCSK9 inhibitors make this therapy inaccessible to the majority of patients in a typical Cardiology practice. The lack of provincial formulary coverage for mAb PCSK9 inhibitors for the ASCVD indication impacts numerous Canadians. As such an additional therapy for Canadians who do not meet treatment goals and who are not able to access mAb- based PCSK9 inhibitors is required.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

PCSK9 proteins play a crucial role in the pathogenesis of atherosclerotic cardiovascular disease. They regulate the expression of LDL receptors on hepatocytes, which are responsible for removing LDL cholesterol from circulation. In individuals with high levels of PCSK9, the degradation of LDL receptors is enhanced, leading to reduced LDL clearance and elevated LDL cholesterol levels. This dysregulation contributes to the development and progression of atherosclerosis, as increased LDL cholesterol promotes the formation of lipid-rich plaques in arterial walls.

There are two distinct approaches to PCSK9 inhibition for the management of hypercholesterolemia: monoclonal antibodies and small interfering RNA (siRNA). Inclisiran is the first treatment in this class that uses siRNA as an approach to reduce LDL-C.

Results from three completed Inclisiran Phase 3 trials in patients with heterozygous familial hypercholesterolemia or ASCVD lowered LCL by 51% and the only notable side effect that was increased relative to placebo was local injection site reactions. Pooled Phase 3 data that examined unadjudicated safety events showed a 26% reduction in the rate of cardiovascular events. Inclisiran's twice-yearly injections provided consistent and persistent LDL-C reduction over 4 years in a reported extension study.

This medication will be used as an add-on to maximally tolerated doses of statins (and/or ezetimibe) in patients who require additional lipid lowering as per the 2021 Canadian Dyslipidemia Guidelines.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Available data indicates the response to Inclisiran is consistent among patient groups, and as such it would be suited to all patients who require additional LDL lowering. Based upon PCSK9 inhibitor data there are patient subsets that would be expected to derive a more pronounced benefit. These patients groups include:

1. Patients with a diagnosis of heterozygous familial hypercholesterolemia

2. Patients with statin intolerance and unable to achieve threshold values on ezetemibe

3. Patients with ASCVD and additional enriching high risk features such as: recent myocardial infarction, recurrent myocardial infarctions, CABG, multi-vessel disease, polyvascular disease and diabetes.

Patients would be identified based on their diagnosis (FH or ASCVD) and the results of lipid testing (LDLC, non-HDL-C, apoB). The lipid assessments are widely available and routinely ordered in clinical practice. There are no issues related to the diagnosis of ASCVD however patients with FH are often under-diagnosed in primary care (15% identified from total Canadian population).

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Response to therapy includes a measurement of the LDL-C, non-HDL-C, and ApoB which is a standard of care in clinical practice and would not vary among physicians. A meaningful response to therapy is the continued reduction in LDL-C in a patient that is on maximal tolerated oral therapy but has an LDL-C value persistently above the treatment threshold. The addition of Inclisiran would be expected to allow most treated patients to achieve the treatment threshold.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Discontinuation could be expected under the following circumstances but would be expected to be rare based upon our current experience with the medication:

1. Intolerability – primarily injection site reaction (3%)

2. Lack of response (not anticipated)

3. Other treatment therapies become available (ie bempedoic acid – although unlikely to be marketed in Canada)

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Since patients with FH and ASCVD are co-managed by both cardiovascular specialists and primary care physicians Inclisiran should be prescribed by both physician groups. This is the standard of care currently with the other commercially available mAb PCSK9 inhibitors and should be no different for the siRNA PCSK9 inhibitor. As per the product monograph, this medication is administered by health care professionals in a clinic setting.

6. Additional Information

N/A

Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   NO

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   NO

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Michael Heffernan

Position: Cardiologist

Date: 09-07-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Jeremy Paikin

Position: Cardiologist

Date: 09-07-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	**Check appropriate dollar range***

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Novartis	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Jan Orfi

Position: Cardiologist

Date: 09-07-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Dr. Michelle Paikin

Position: Cardiologist

Date: 09-07-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Qin Li

Position: Cardiologist

Date: 09-07-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Dr. Sean Jedrzkiewicz

Position: Cardiologist

Date: 09-07-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 6: Conflict of Interest Declaration for Clinician 6

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: Dr. David McConachie

Position: Cardiologist

Date: 09-07-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 7: Conflict of Interest Declaration for Clinician 7

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 8

Name: Dr. Vera Chiamvimonvat

Position: Cardiologist

Date: 09-07-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 8: Conflict of Interest Declaration for Clinician 8

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 9

Name: Dr. Shoaib Shy Amiani

Position: Cardiologist

Date: 09-07-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 9: Conflict of Interest Declaration for Clinician 9

Company	Check appropriate dollar range*

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Novartis	X			

* Place an X in the appropriate dollar range cells for each company**CADTH Reimbursement Review Clinician Group Input**

Clinician Group Input

CADTH Project Number: SR0791-000

Generic Drug Name (Leqvio): Inclisiran

Indication: Primary Hyperchlosterolemia

Name of Clinician Group: Internal Medicine Department and Heart failure group St. Thomas Elgin General Hospital (STEGH)

Author of Submission: Drs. Andros, Chehadi, Cieslak

1. About Your Clinician Group

We are practicing physicians as well as hospital physician leaders - Chief of Medicine (Andros), Chief of Staff (Chehadi) and Chief of Hospital Medicine (Cieslak) - and are submitting this report on behalf of our entire group practice of 14 community internal medicine physicians including various subspecialties such as nephrology, hepatology, endocrinology and cardiology. In addition to this we have a community based heart function, cardiovascular and stroke program serving Elgin county.

2. Information Gathering

Information was collected via direct group discussion based on our objective EMR review of patients with hyperlipidemia as well as discussion surrounding our anecdotal experience in managing such patients. We also reviewed the hospitals Quality Improvement Plan (QIP) metrics and re-admission data from CIHI.

3. Current Treatments and Treatment Goals

Hyper lipidemia remains, perhaps, the most elusive of the cardiovascular risk factors to treat. The burden of cardiovascular disease and stroke alone is substantial and is only set to increase. I'm sure many other submissions will also speak to the disease burden, prevalence and projected associated costs, however we feel we bring a slightly different viewpoint in that we can also speak to the direct effects and costs to hospitals through our roles which involve regularly reviewing the Hospitals QIP and readmission data and have all either created or participated in quality improvement projects to address these problems.

In 2017, STEGH identified that our readmission rates were highest for patients with CHF and COPD and were in fact some of the highest rates in the country at approximately 25%. We then sought to undertake a QI project through the IDEAS program aimed at lowering such rates and thus developed the PREVENT program (Preventing Readmissions in Elgin county through Novel Transitions), which in the first year of implementation was able to reduce readmission rates for both HIGS conditions (COPD and CHF) to 14 and 15% respectively. We also identified through a QI project that there was opportunity to improve the care provided through closer alignment to goal directed medical therapies which we also pursued at the same time.

Despite these, and 8 years later, we still have readmission rates in the 15-20% range for heart failure, despite a substantial improvement in the alignment with guideline based therapies. These persistently high readmissions, coupled with the continued increases in the incidence and prevalence of cardiovascular disease and stroke continues to put substantial strain on our hospital resources and emergency departments and likely the same is true for every other hospital in the province as well.

Hyperlipidemia is of course a critical risk factor in the management of CVD and stroke and is perhaps the hardest to treat of all of them. Current treatments include Statins, Ezetrol and other older various agents with somewhat intolerable side effects or limited efficacy (eg. Fibrates, bile acid sequestrates). Statins are unquestionably the most effective of the above agents and have a durth of evidence to support their use, however in practice it is quite challenging to not only get patients up to the maximum dose but often to have them agree to their use in the first place. More often then not we have to settle for the maximum tolerated dose which is often set by side effects, be it real or perceived. In Elgin county and particularly Aylmer, there is a high resistance to 'conventional medicine' and we are acutely aware of the concerted effort of the 'natural health' industry both locally and broadly to undermine the use of statins in particular.

In the last few years our use of Inclisiran and the PCSK9 inhibitors Repatha and Praluent has grown and we have found them to be remarkably effective in meeting lipid treatment goals for patients also taking statins (FH aside). We also have used it in patients with primary genetic disorders of lipid metabolism and also have found them to be extremely effective. Anecdotally, we have noticed that the frequency of secondary CVD events has also decreased and look forward to objective data once our sample size becomes large enough.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

As alluded to in section 3, a large patient population have true or perceived intolerances to the current standard of lipid lowering therapy (statins) and/or have an adversity towards being placed on this effective class of medication due to misinformation from various platforms (eg social media).
As a result, several of our CAD patients are not meeting CCS targeted guidelines of LDL's 1.8mmol/L or less. Since the COVID-19 pandemic, we have noticed a substantial increase in the number of our patients with ASCVD who are not even close to target LDL, including those who are willing/able to take statins at the maximal tolerated dose.

Several of these patient include high-risk patients with a history of recurrent CAD (with or without previous PCI or revascularization). Several patients who have experienced recurrence of ASCVD are also on maximal tolerated statin therapy as well as Ezetemibe.

Compliance is always a concern with any medication. One of the nice things about Inclisiran is that it is only a twice yearly administered medication that is given by a healthcare professional essentially eliminating any uncertainty of non-compliance.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

The extreme effectiveness of PCSK9 inhibitors in conjunction with statins and even as mono-therapy, significantly drives down a patient's LDL. We know that there is no bottom limit to an LDL and that in fact an LDL of 1.4mmol/L or less can actually lead to plaque regression. This is what we feel is one of Inclisiran's biggest strengths.

Through Inclisiran's mechanism of action by targeting the synthesis of the PCSK9 enzyme (as opposed to simply inhibiting the receptor alone with antibody as per mechanism of action of Repatha and Praluent) it most certainly addresses and impacts the underlying disease process of ASCVD as opposed to being a symptomatic management therapy.

Truthfully, we would love to see PCSK9 inhibitors as first-line therapy one day in the future however fiscal responsibility in today's difficult economic times and on our significantly strained Canadian health care system is important. In that light, we don't see Inclisiran becoming a first line therapy any time soon. With that said, if a pilot study was performed looking at the cost savings to the healthcare system with reduced readmission rates and reduced incidence of ACS as a result of the more aggressive and pronounced lipid lowering therapy, this could in fact offset the cost of the drug. At the current time however, we see Inclisiran as an excellent add-on therapy to standard treatments of statin and Ezetemibe when LDL targets are not being met.

We feel Inclisiran should not be reserved just for those who are intolerant of other treatments or whom treatments are contraindicated, as the most benefit would be gained by highest risk patients (those with recurrent ASCVD with other CAD risks factors present eg DM, HTN).

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Patients who are not meeting targets with an established history of ASCVD, particularly those with recurrence of disease and/or ongoing symptoms of chest pain. Patient's with high risk lesions and those with pre-existing moderate to severe heart failure secondary to ischemic heart disease are who we feel are most in need of Inclisiran and who would benefit the most.

Additional disease characteristics and/or co-morbid CAD risk factors (eg poorly controlled diabetes and hypertension) would more likely than not benefit further.

Patients who would be considered best suited for Inclisiran could be easily identified through clinical examination (hypertension, evidence of heart failure eg peripheral edema), laboratory tests (most notably LDL, Apo-B, LipoproteinA and HbA1c) and more sensitive diagnostic testing including SESTAMIBI myocardial perfusion scan, CT coronary angiography and of course invasive cardiac angiography.

We do not foresee any issues related to diagnosis.

Misdiagnosis would really only occur if the above listed laboratory and diagnostic testing were not performed.

Although we feel all patients with established and diagnostically proven ASCVD would benefit from Inclisiran, it is possible to identify those patients who are most likely to exhibit a response to treatment based on their angiography results, control of other CAD risk factors (eg diabetes and hypertension) and of course symptoms.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Outcomes in clinical practice are very much aligned with outcomes typically used in clinical trials.
This holds even more true as it relates to our practice as community specialists where patients are being assessed and examined by ourselves and treatment/management decisions are carried out by us personally (in conjunction with shared patient decision making and buy-in).

Clinically meaningful response would be:

- Achieving an LDL of at least 1.80 mmol/L or less (preferably less than 1.40 mmol/L)
- Improved survival
- Reduction in recurrence of ASCVD and acute coronary syndromes includes reduction in admission rates to hospital
- Improvement of symptoms (eg more exertion required before onset of chest pain symptoms leading to improved quality of life)
- Less progression to heart failure as a results of ischemic heart disease
- Objective measurement and identification of plaque regression

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Factors to be considered when deciding whether to discontinue Inclisran would be intolerable adverse effects to the drug and/or a true allergy. Otherwise the expectation would be to stay on the drug indefinitely as the benefit would be long term.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

All settings where ASCVD patients might be assess would be appropriate for treatment with Inclisiran. This includes community hospital and outpatient settings, academic/tertiary hospital settings and all specialty clinic settings with those familiar in assessing and managing patients with ASCVD.

This would include Internal Medicine, Cardiology, Neurology and Vascular surgery specialties.

6. Additional Information

None

Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   We received data support through the Transforming Care Office at STEGH.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. P Andros
Position: Chief of Medicine
Date: 11-07-2023

X **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Boehringer Ingelheim	X			
Novartis	X			
Pfizer	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. W. Chehadi
Position: Chief of Staff
Date: 11-07 -2023

X I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Pharma Science	X			
Boehringer Ingelheim	X			
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Martin Cieslak
Position: Chief of Hospitalist Medicine
Date: 11-07-2023

X I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				
None				
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: <Enter full name>
Position: <Enter currently held position>
Date: <DD-MM-YYYY>

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**

Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: <Enter full name>
Position: <Enter currently held position>
Date: <DD-MM-YYYY>

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Clinician Group Input

CADTH Project Number: SR0791-000

Generic Drug Name (Brand Name): inclisiran

Indication: Primary hypercholesterolemia

Name of Clinician Group: Western University, Division of Cardiology, Cardiac Rehabilitation and Secondary Prevention Program

Author of Submission: Dr. Neville Suskin, Dr. Robert McKelvie & Dr. Ashlay Huitema

1. About Your Clinician Group

Comprehensive cardiac rehabilitation including secondary prevention care delivery

2. Information Gathering

Literature review, group experience including program evaluation and publications

3. Current Treatments and Treatment Goals

Annually, approximately 90,000 patients in Ontario and 250,000 patients in Canada are diagnosed with atherosclerotic cardiovascular disease (ASCVD), and as such are eligible for drug treatment for lipids to achieve LDL-C < 1.8 mmol/L as per the latest Canadian dyslipidemia guidelines (DOI: 10.1016/j.cjca.2018.07.413 & 10.1016/j.cjca.2021.03.016). In addition to prioritizing healthy lifestyle interventions, the use of pharmacotherapeutic options to treat eligible patients is recommended by the Canadian 2021 dyslipidemia guidelines to further reduce morbidity and mortality from ASCVD in Canada (DOI: 10.1016/j.cjca.2021.03.016).

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

In the real-world Canadian context lipid management is unsatisfactory. From 2010 to 2017, less than 30% of the 280,000 ASCVD patient cohort were taking the recommended dose intensity of statins and 34% were not taking statins at all (Chen et al, Can J Cardiol, 2019;35:884-891). Within 6-months following percutaneous coronary intervention between 2011 & 2014, only 52% of almost 48,000 patients in Ontario had their LDL-C measured, and 43% of those had LDL-C > 1.8 mmol/L. Compared to patients with LDL-C < 1.8 mmol/L, patients with LDL-C 1.8-2.6 & > 2.6, experienced MACE rates that were 20 & 80% higher respectively (Sud M et al. J Am Coll Cardiol. 2020; 76:1440-1450).

In our large (> 1,000 referrals annually) clinical cardiac rehabilitation practice, most patients are referred following a recent ACSVD event or procedure. At cardiac rehabilitation intake, which generally takes place within 2 months of the ASCVD event, 50% of patients have LDL-C values above 1.8 mmol/L. Six months later at cardiac rehabilitation program graduation, the proportion of patients remaining above the LDL-C target of 1.8 mmol/l is about 30%, and consequently these patients remain eligible for additional lipid lowering therapies according to the latest Canadian guidelines. This is despite our best efforts with lifestyle and behaviour change counseling along with aggressive implementation of available combination lipid lowering therapies. Consequently, treatments and treatment strategies are needed to reduce this care-gap.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Inclisiran is approved by Health Canada as an adjunct to lifestyle changes, with or without other LDL-C -lowering therapies, to further reduce LDL-C in adults with heterozygous familial hypercholesterolemia (HeFH) or hypercholesterolemia with atherosclerotic cardiovascular disease.

In real-world practice, as supported by guidelines, we anticipate inclisiran as an add on to maximally tolerated statin therapy in eligible patients.

We have received positive feedback from our patients for government funded emerging lipid-lowering maintenance therapies that would only be given every 6 months. Thus, inclisiran provides a novel alternative to existing PCSK9-inhibitor therapy as inclisiran has the potential to dramatically improve adherence to therapy

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

All eligible patients adhering to appropriate healthy lifestyle choices, who do not have LDL-C levels below treatment intensification thresholds despite maximally tolerated statin therapy, would benefit from inclisiran therapy.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Typically, confirmation of treatment adherence and LDL response is used to determine meaningful responses to therapy.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Adverse effects.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Any prescribing health care practitioner could prescribe inclisiran for eligible patients.

6. Additional Information

The ORION-3 extension trial (doi.org/10.1016/S2213-8587(22)00353-9), inclisiran maintained a significant 44% LDL-C reduction with reductions in PCSK9 ranging from 62% to 78% through 4 years in 382 patients with atherosclerotic CV disease and those with an atherosclerotic disease equivalent. This finding is in addition to aggressive background therapy (e.g., statin or ezetimibe) to lower LDL-C. Inclisiran therapy was proven to be well tolerated and safe.

Another recent study reported on a prespecified patient level pooled analysis of the ORION-9, -10, and -11 studies involving 3660 patients with heterozygous familial hypercholesterolemia, ASCVD, or ASCVD risk equivalent followed for 18-months. The prespecified outcome was a MACE composite of cardiovascular death, cardiac arrest, non-fatal myocardial infarction, and fatal and non-fatal stroke. Inclisiran significantly reduced the prespecified MACE outcome by 26% (doi.org/10.1093/eurheartj/ehac594). The accompanying editorial (doi.org /10.1093/eurheartj /ehac594) described these results (MACE reduction and safety profile) as reflecting similar beneficial trends to the PCSK9 inhibitor and genetic studies supporting the value of PCSK9 inhibition, and we concur with this sentiment.

These data are consistent with multiple lines of evidence demonstrating the benefit of lowering LDL-C appears to be independent of the mechanism by which LDL-C is lowered. The data from the patient level pooled analysis study for inclisiran would further support the statement. In fact, the number of MACE events in the inclisiran pooled data analysis study is substantially greater than the comparable analyses of the Phase III trials with PCSK9 inhibitors that preceded the outcome trials for those therapies (DOI: 10.1056/NEJMoa1500858 & DOI 10.1056/NEJMoa1501031)

We, and others, anticipate that getting Inclisiran to market would supply healthy competition for other PCSK9 pathway therapies, and as such may well lower the price points for these therapies. Thus, the fact there is not direct comparative evidence for inclisiran versus PCSK9 inhibitors should not influence your final recommendation.

Therefore, based on the available evidence, we believe that inclisiran should be recommended for funding. This will allow the large number of patients at significant residual cardiovascular risk with elevated LDL-C, despite receiving aggressive lipid lowering therapy, access to medical therapy that has been proven to safely further lower LDL-C. Importantly, the fact inclisiran is administered every 6 months would potentially improve patient compliance.

Conflict of Interest Declarations

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1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Neville Suskin

Position: Professor of Medicine, Div. Cardiology, Western University, Ontario, Canada

Date: 10-07-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis (consultancy)			X ($11,090)	
Sanofi (speaker)	X			
HLS (ad. Board/grant)	X		X ($25,000)	
Boehringer Ingelheim (grant)			X ($25,000)	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Robert McKelvie

Position: Professor of Medicine, Div. Cardiology, Western University, Ontario, Canada

Date: 10-07-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis		x		
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Ashlay Huitema

Position: Assistant Professor of Medicine, Div. Cardiology, Western University, Ontario, Canada

Date: 10-07-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Amgen	X			
Bayer	x			
Boehringer Ingelheim	x			

* Place an X in the appropriate dollar range cells for each company.

Clinician Group Input

CADTH Project Number: **SR0791-000**

Generic Drug Name (Brand Name): **Inclisiran (Leqvio)**

Indication: **As per the Health Canada approved indication, for primary hypercholesterolemia (Heterozygous familial hypercholesterolemia (HeFH) and non-familial hypercholesterolemia (nFH)) with atherosclerotic cardiovascular disease (ASCVD)**

Name of Clinician Group: **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.**

Author of Submission: **Dr Lawrence A Leiter**

1. About Your Clinician Group

We are Faculty at the University of Toronto (https://www.utoronto.ca/about-u-of-t) and clinicians at St Michael's Hospital-Unity Health Toronto (https://unityhealth.to/locations/st-michaels-hospital/) who are actively involved in the treatment of patients with atherosclerotic cardiovascular disease (ASCVD) and/or lipid disorders in order to reduce their risk of having a (recurrent) vascular event.

2. Information Gathering

This submission is based on published data and our clinical experience.

3. Current Treatments and Treatment Goals

Cardiovascular (CV) disease (CVD) remains a major cause of morbidity and mortality in Canada and lowering and optimizing LDL-C is an essential component of our risk reduction strategies. Health behaviour modification and statins remain the initial treatment of patients with elevated low-density lipoprotein cholesterol (LDL-C) levels, but our current (2021) Canadian Cardiovascular Society Guidelines recommend that, in our patients with known ASCVD, additional non-statin agents be added if the LDL-C remains greater than 1.8 mmol/L despite being on maximally tolerated statin therapy. If the LDL-C is between 1.8 and 2.2 mmol/L, the Guidelines recommend the addition of ezetimibe as the next step whereas if the LDL-C is greater than 2.2 mmol/L, it is recommended that a PCSK9 inhibitor (with or without ezetimibe) be added. The monoclonal antibodies to PCSK9, evolocumab and alirocumab, lower LDL-C by an additional 60% and have been shown in large outcome studies to significantly reduce the risk of CV morbidity and mortality, with excellent safety and tolerability profiles.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

A number of recent Canadian population-based, real-world studies have demonstrated that many high CV risk patients continue to have LDL-C levels well above the Guidelines recommended LDL-C threshold of 1.8 mmol/L (*Sud et al J Am Coll Cardiol 2020;76:1440-50; Sarak et al Circulation: Cardiovascular Quality and Outcomes 2021;14:e006646*). This is a result of multiple factors including insufficient LDL-C lowering with statins (with or without ezetimibe), statin-associated side effects, suboptimal medication adherence, and treatment inertia. The addition of the PCSK9 monoclonal antibodies can bring the LDL-C levels below threshold in the vast majority of these patients. Nonetheless, many appropriate patients are not receiving these agents. Cost and access remain major barriers. These drugs are not covered for public reimbursement in Canada for patients with ASCVD, except in those patients who have FH. In addition, some patients will decline the use of the drugs because they are self-administered subcutaneous injections every 2-4 weeks. Over the years, individual cases of suboptimal LDL-C lowering or complete intolerance to both monoclonal agents are increasingly recognized. The availability of an additional PCKS9 inhibitor treatment option with improved access and less frequent administration would be a most welcome addition and would help to get the LDL-C of more of these high CV risk patients to below threshold values. This would, in turn, significantly reduce major adverse cardiovascular events (MACE), including myocardial (re-)infarction, ischemic stroke, the need for coronary revascularization (percutaneous coronary intervention/stenting and coronary artery bypass surgery), and cardiovascular death.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Inclisiran is a small interfering RNA (siRNA) drug that in phase 3 trials was shown to reduce LDL-C levels by about 50% with a safety profile that is similar to the PCSK9 monoclonal antibodies (the only treatment emergent adverse event more frequently seen with inclisiran vs. placebo being a small increase in local injection site reactions, none of which were severe or persistent) (*Wright et al. J Am Coll Cardiol. 2021;77:1182*). Although this subcutaneously administered drug (by healthcare providers instead of patient self-administration) is cleared from the blood stream within 48 hours, it has a prolonged action in the liver where it decreases the synthesis of naturally made PCSK9, allowing for infrequent dosing (injections every 6 months after the initial and 3-month dose). Two large CV outcome studies are underway so MACE information is not likely to be available sooner than 2026; however, [redacted] While the previous phase 3 trials demonstrating significant efficacy in LDL-C lowering and excellent safety up to 18 months were not powered to assess MACE, a pooled analysis of the safety reports in these studies has revealed a significant 26% reduction for MACE with inclisiran compared to placebo (with the vast majority receiving background statin therapy) (*Ray et al. Eur Heart J. 2023;44:129*). It should also be noted that we now have evidence with 5 different classes of drugs (bile acid sequestrants, statins, ezetimibe, monoclonal antibodies to PCSK9, and bempedoic acid) that lower LDL-C (similar to inclisiran) that have all shown CV benefit. Furthermore, in a pooled safety analysis of inclisiran in 3,576 patients with approximately 10,000 person-years of exposure from seven trials with a mean duration of follow-up of 2.8 years (and 43% of patients on the drug for >3 years), no new safety signals were detected (*Wright et al J Am Coll Cardiol. 2023;81(Suppl.):1626*). Thus, inclisiran would provide an additional treatment option that requires less frequent dosing which may lead to better medication adherence and perhaps greater accessibility than the monoclonal antibody PCSK9 inhibitors.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

In addition to that outlined in Section 5.1, the Canadian Cardiovascular Society Lipid Guidelines (*Pearson et al Can J Cardiol. 2021;37:1129-1150*) – which are based on many published subgroup analyses of the PCSK9 monoclonal antibody CV outcome trials – strongly recommend intensification of lipid-lowering therapy with a PCSK9 inhibitor (with or without the additional use of ezetimibe) for secondary CV prevention patients shown to derive the largest benefit from PCSK9 inhibitor therapy in whom LDL-C remains at 1.8 mmol/L and higher (or non-high-density lipoprotein cholesterol [non-HDL-C] 2.4 mmol/L or higher, or apolipoprotein B (ApoB) 0.7 g/L or higher) while receiving the maximally tolerated statin dose. The patients who experience similar relative, but greater absolute, benefit from PCSK9 inhibition include those with:

- A recent acute coronary syndrome (ACS) event (particularly those hospitalized within the previous year)
- Clinically evident ASCVD and any of the following
  - Diabetes mellitus or metabolic syndrome
  - Polyvascular disease (vascular disease in ≥ 2 arterial beds)
  - Symptomatic peripheral artery disease (PAD)
  - Recurrent MI
  - MI in the past 2 years
  - Previous CABG surgery
  - LDL-C ≥2.6 mmol/L or heterozygous FH
  - Lipoprotein(a) ≥60 mg/dL (120 nmol/L)

Indeed, the guidelines identify those at particularly high risk who would derive greater absolute benefit (with corresponding lower Numbers-needed to treat [NNT]) and therefore greater clinical benefit in a more (than all ASCVD patients) cost-effective manner.

In addition to the above, inclisiran could also be considered for individuals who are intolerant to the PCSK9 monoclonal antibodies, those with learning disabilities (e.g. attention deficit/hyperactivity disorder), and patients who are uncomfortable with or cannot self-inject.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

The maximum LDL-C lowering of inclisiran is typically achieved by about 90 days. As with other lipid-lowering drugs, treatment efficacy will be monitored by measuring LDL-C, typically every 6 to 12 months. As noted above, sustained lowering of LDL-C is required to achieve maximum CV benefit.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

None

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

The specific indication (high CV risk patients with elevated LDL-C despite lifestyle and maximal tolerated statin dose plus ezetimibe) simple dosing of inclisiran, and straightforward safety and tolerability profile should allow for the drug to be prescribed by either primary care or specialist physicians.

6. Additional Information

None

Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Lawrence A. Leiter

Position: Professor of Medicine and Nutritional Sciences, University of Toronto; Director, Lipid Clinic, St. Michael's Hospital-Unity Health Toronto

Date: 15-06-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis			X	

Declaration for Clinician 2

Name: Alice Y. Y. Cheng

Position: Associate Professor of Medicine, University of Toronto; Endocrinologist, St. Michael's Hospital-Unity Health Toronto and Trillium Health Partners,

Date: 15-06-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	X ($0)			

Declaration for Clinician 3

Name: Shaun G. Goodman

Position: Professor of Medicine, University of Toronto; Associate Head, Division of Cardiology, St. Michael's Hospital-Unity Health Toronto; Adjunct Professor of Medicine, University of Alberta

Date: 16-06-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis			X (for consulting and Executive Steering Committee activities in the VICTORION-2P trial of inclisiran vs. placebo)	

Declaration for Clinician 4

Name: Subodh Verma

Position: Professor of Surgery, and Pharmacology and Toxicology; Cardiac Surgeon, St. Michael's Hospital-Unity Health Toronto; Canada Research Chair in Cardiovascular Surgery, University of Toronto

Date: 16-06-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis		X		

Declaration for Clinician 5

Name: Cynthia T. Luk

Position: Assistant Professor of Medicine, University of Toronto; Endocrinologist, St. Michael's Hospital-Unity Health Toronto

Date: 17-06-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	X			

Declaration for Clinician 6

Name: Bobby Yanagawa

Position: Associate Professor of Surgery, University of Toronto; Cardiac Surgeon, St. Michael's Hospital-Unity Health Toronto

Date: 18-06-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 6: Conflict of Interest Declaration for Clinician 6

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	X			

Declaration for Clinician 7

Name: Dominic S. Ng

Position: Associate Professor of Medicine, Physiology and Laboratory Medicine and Pathobiology, University of Toronto; Endocrinologist, St. Michael's Hospital-Unity Health Toronto

Date: 18-06-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 7: Conflict of Interest Declaration for Clinician 7

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	X			

Declaration for Clinician 8

Name: Beth L. Abramson

Position: Associate Professor of Medicine, University of Toronto; Cardiologist, St. Michael's Hospital-Unity Health Toronto

Date: 18-06-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 8: Conflict of Interest Declaration for Clinician 8

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis		X For Advisory Boards and speaker for Educational Programs		

Declaration for Clinician 9

Name: John L. Sievenpiper

Position: Professor of Nutritional Sciences and Medicine, University of Toronto; Staff Physician, Division of Endocrinology and Metabolism, St. Michael's Hospital-Unity Health Toronto

Date: 19-06-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 9: Conflict of Interest Declaration for Clinician 9

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	X ($0)			

Declaration for Clinician 10

Name: Kim A. Connelly

Position: Professor of Medicine and Physiology, University of Toronto; Division Head of Cardiology, St. Michael's Hospital-Unity Health Toronto; Executive Director of Keenan Research Center for Biomedical Science, Li Ka Shing Knowledge Institute, St. Michael's Hospital

Date: 20-06-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 10: Conflict of Interest Declaration for Clinician 10

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	X ($0)			