CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

inclisiran (Leqvio)

(Novartis Pharmaceuticals Canada Inc.)

Indication: Leqvio 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 (HeFH), or
- Non-familial hypercholesterolemia with atherosclerotic cardiovascular disease

The effect of Leqvio on cardiovascular morbidity and mortality has not been determined.

September 23, 2021

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0681 Leqvio
Brand name (generic)	Leqvio (inclisiran)
Indication(s)	Primary hypercholesterolemia
Organization	Western University, Division of Cardiology, Cardiac Rehabilitation and Secondary Prevention Program, London, Ontario
Contact information[a]	Name: Robert McKelvie MD PhD FRCPC [redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

We don't agree with the recommendation reached by the CADTH CDEC stating that Inclisiran should not be reimbursed to further reduce low-density lipoprotein cholesterol (LDL-C) level in adults with HeFH or nHF with ASCVD who are on a maximally tolerated dose of statin, with or without other LDL-C lowering therapies. Inclisiran has been approved by Health Canada for these very indications.

In the ORION trials, Inclisiran significantly reduced LDL-C in 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 has proven to be well tolerated and safe.

In our large clinical cardiac rehabilitation practice, despite our best efforts with lifestyle modification and available combination lipid lowering therapies, 20% of patients remain eligible for added lipid lowering therapies according to the latest Canadian Lipid guidelines. Moreover, we have informally received positive feedback from patients for emerging lipid-lowering therapies that are only required to 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.

Multiple lines of evidence have demonstrated the benefit of lowering LDL-C appears to be independent of the mechanism by which LDL-C is lowered. Therefore, we think it is justifiable to extrapolate that Inclisiran, because it so significantly reduces LDL-C, will also result in a reduction of CV events.

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 PCSK9i should not influence the 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 CV 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.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

If not, what aspects are missing from the draft recommendation?

I can't say our input was considered because this is the first time we have reviewed the document.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒

If not, please provide details regarding the information that requires clarification.

It didn't appear to us that the input from the patient group, clinician, and clinician group was as negative towards the drug as would have been expected based on the recommendations. In effect in our opinion the input seemed to be more in favour of the potential usefulness of the drug.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒

If not, please provide details regarding the information that requires clarification.

We don't think implementation was clearly addressed probably because the recommendation did not support funding of the therapy.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒

If not, please provide details regarding the information that requires clarification.

We don't think reimbursement conditions were clearly stated because the recommendation was to not fund the therapy.

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- 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 feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please 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 declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Please state full name* Robert McKelvie MD PhD FRCPC
Position	*Please state currently held position* Professor of Medicine (Cardiology) Western University, London, Ontario
Date	*Please add the date form was completed (21-09-2021)*
☒	**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				
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.				
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	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Please state full name* Neville Suskin MD MSc FRCPC
Position	*Please state currently held position* Associate Professor of Medicine (Cardiology) Western University, London, Ontario
Date	*Please add the date form was completed (21-09-2021)*
☒	**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				
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.				
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	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Please state full name* Ashlay Huitema MD FRCPC
Position	*Please state currently held position* Associate Professor of Medicine (Cardiology) Western University, London, Ontario
Date	*Please add the date form was completed (21-09-2021)*
☒	**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				
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.				
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	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (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.

Conflict of Interest Declaration

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.

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (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.

Conflict of Interest Declaration

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.

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	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	UNCERTAIN
Brand name (generic)	Inclisiran
Indication(s)	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
Organization	Service de cardiologie et Clinique de lipides du Centre Hospitalier Universitaire Dr-Georges-L.-Dumont
Contact information[a]	Name: Dr Luc Cormier

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

Specifically, there are 2 main indications why we disagree with the recommendation:
For the HeFH population, all clinical trials have been designed to reduce LDL-C which is the main driver for CV risk in this "very high risk" population. The data specifically with Inclisiran published to date does show significant LDL reduction in a margin comparable to high potency LDL-C reduction treatments such as statins and PCSK-9 inhibitors. As such, this is consistent with all previous therapies specifically designed to reduce LDL-C.

As clinicians, we need more tools for treatment of high LDL-C. Furthermore, CDEC mentions that there are no comparison trials with PCSK-9 inhibitors nor any CV risk reduction to justify treating LDL-C reduction with Inclisiran rather than PCSK-9 inhibitor. We agree with this statement, but however, the reality of our Canadian setting, is that there is very low penetrance of PCSK-9 inhibitor use due to poor access for various reasons (our estimate is that use is less than 5% of potential patients, and we are very pro-active as a group to initiate PCSK-9 inhibitors). When feasible to have access to PCSK-9 inhibitors (rare), it is very complicated to enroll patients, initiate therapy, and ensure therapy persistence for various reasons. 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.

Furthermore, we comment on the "key limitations" noted in the "Economic evidence" table :

- *"The effect of inclisiran on cardiovascular outcomes is highly uncertain. The predicted survival benefit for patients treated with inclisiran has not been shown in clinical trials. The sponsor's model used a surrogate outcome, LDL-C, to approximate the relationship between treatment and cardiovascular risk."*

  In the era of trial using statins only, there was no other lipid therapy other than statins that had an effect on CV risk. However, since then, even modest potency treatments were associated with CV risk reduction (ezetimibe), as well as other medications with greater potency (PCSK-9 inhibitors). All LDL reductions have shown an CV risk reductions correlating to the Cholesterol Treatment Trialists analyses. In such, one cannot say that the expected effect of inclisiran is "highly" uncertain, but that further data will confirm the expected CV risk reduction as per LDL-C lowering.

- *"The comparative clinical effectiveness of inclisiran versus PCSK9 inhibitors is highly uncertain. There have been no head-to-head trials of inclisiran versus PCSK9 inhibitors, and there is substantial uncertainty in the results of the sponsor's network meta-analyses."*

  Again, the indication for use of inclisiran is not as a replacement of PCSK-9 inhibitors. Furthermore, PCSK-9 inhibitors have not proven to be a treatment that is accessible to most Canadians at significant CV risk, and as such should not be considered a standard of care or benchmark given its limited use or access. In this sense, clinical effectiveness of Inclisiran should not rely on a comparator other than what is considered standard of care (use of PCSK-9 inhibitor again is not a clinical standard).

- *"The sponsor considers relative, but not absolute, changes in LDL-C levels. The clinical expert consulted by CADTH for this review indicated that absolute changes may be a more relevant measure of effect for patients with HeFH."*

  Both data can be used and are available and significant (as per your clinical expert), so why is this considered a "key limitation".

- *"The baseline risk of cardiovascular events in the modelled population may not reflect risk in the Canadian population." AND "The sponsor employed poor modeling practices in their model, preventing CADTH from fully validating the model and its findings."*

  Some type of model should be used. Why doesn't the modelled population used reflect baseline Canadian population CV risk? If CADTH has a standard model that should be used, CADTH should provide the suggested model to use or propose re-analysis with a model that it considers would better "reflect risk in the Canadian population".

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒
If not, what aspects are missing from the draft recommendation? As far and wide is Canada, it is also diverse in its populational makeup, its socioeconomic realities, and institutional capabilities. As such, we consider that CDEC did not elect to involve clinician groups that represent pan-canadian realities adequately, especially in regards to lipid management and CV risk reduction which is a wide reaching and important topic. In this sense, the British Columbia-centric clinician group that does not include other Canadian realities, which could have even further emphasized the urgency to get access to other treatment tools in lipid management elsewhere in Canada. Furthermore, we note that there was only one clinician expert input. Again, the topic of lipid management is very wide reaching and should include many clinician experts, especially in the clinical cardiology field which does not appear to have been well represented in CDECs process.		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification. They have not been addressed and as such, likely to limitation due to implementation have been noted by CDEC.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification. Not clearly stated since it was recommended against reimbursement.		

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☒
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed:		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Dr Luc Cormier*
Position	*Lipid clinic director, and clinical cardiologist, CHU Dr-Georges-L-Dumont (Moncton, NB)*
Date	*2021-09-15*
☒	**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

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.

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	☐	☒	☐	☐
Amgen	☐	☒	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Dr Michel D'Astous*
Position	*Coronary Care Unit Director, CHU Dr-Georges-L-Dumont*
Date	*2021-09-15*
☒	**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

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.

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Dr Jean-François Baril*
Position	*Chief of Cardiology, CHU Dr-Georges-L-Dumont*
Date	*2021-09-15*
☒	**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				
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.				
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	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Dre Rina Lee*
Position	*Cardiovascular clinical trials director, and clinical cardiologist CHU Dr-Georges-L-Dumont*
Date	*2021-09-15*
☒	**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				
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.				
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	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Dre Stéphanie Thébeau*
Position	*Clinical cardiologist*
Date	*Please add the date form was completed (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.

Conflict of Interest Declaration				
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.				
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	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	
Brand name (generic)	**INCLISIRAN**
Indication(s)	Primary hypercholesterolemia
Organization	TotalCardiology Rehabilitation
Contact information[a]	Name: Sandeep Aggarwal

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒
Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.		

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

If not, what aspects are missing from the draft recommendation?
The evidence that lower LDL reduces cardiovascular risks is proven beyond a doubt. In addition, new Canadian lipid guidelines have suggested that there is no lower limit and that benefit continues to accrued as the LDL is lowered even as low as 0.5mmol/L. Inclisiran is as effective as effective as PCSK9i's in lowering LDL. The data for PCSK9is was also clear that it reduced cardiovascular endpoints. Inclisiran will be 30% cheaper than PCSK9is and likely after negotiation with the provinces (which will inevitably occur) will mimic the cost that the UK was able to get for their population. As such the cost will be much lower than you have calculated. In addition, the change from using PCSK9i to Inclisiran for FH by each provincial plan will result in a cost savings.

Your economic calculations do not take into account those that cannot take statins or other lipid lowering medications. This is not a large population but if they have ASCVD their risk without any lipid lowering is high. Coverage for PCSK9i has not been approved for ASCVD and therefore a choice is needed for this group. CADTH should recalculate the cost effectiveness in this population.

Our group of cardiac rehabilitation physicians who manage 1800 to 2000 ASCVD patients a year believe there is a significant gap in care that could be helped with the coverage of this agent by the provincial plans.

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒

If not, please provide details regarding the information that requires clarification. I disagree that laboratory assessments are not appropriate for assessing effectiveness in the real world. That is how we assess effectiveness in the real world. This is not clear what is meant by this statement.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification. I am not sure what part of the document this refers to since the recommendation by CADTH was to not reimburse		

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- 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.
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- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*TotalCardiology Rehabilitation*
Position	
Date	*Please add the date form was completed (09-20-2021)*
☐	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.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

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.

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

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- 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.
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  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
3. Did you receive help from outside your clincian group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☒
	Yes	☐

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Sandeep G. Aggarwal*
Position	*Medical Program Director TotalCardiology*
Date	*Please add the date form was completed (09-20-2021)*
☒	**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				
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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	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Ronak Kanani*
Position	*Cardiologist*
Date	*Please add the date form was completed (09-20-2021)*
☒	**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

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.

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Andrew Dottridge*
Position	*Family Practioner*
Date	*Please add the date form was completed (09-20-2021)*
☒	**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

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.

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Andy Westib*
Position	*Cardiologist*
Date	*Please add the date form was completed (09-20-2021)*
☐	**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				
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.				
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	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0681-000
Brand name (generic)	Inclisiran
Indication(s)	Leqvio
Organization	BC Lipid Specialists
Contact information[a]	Name: Liam Brunham

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

We respectfully disagree with the Committee's recommendation. As the only clinician group to provide input on this medication, and as a group of specialist physicians who manage patients with hypercholesterolemia on a daily basis, we feel that the recommendation is inappropriate for the following reasons:

- As stated in our input, there is a great unmet need for LDL cholesterol lowering in patients with atherosclerotic cardiovascular disease or Heterozygous Familial Hypercholesterolemia (HeFH)
- Existing therapies are inadequate because of poor adherence (statins), low efficacy (ezetimibe), and lack of access/high cost (PCSK9 monoclonal antibodies)
- Inclisiran has the potential to address many of these issues and provide a much needed new option for patients who require additional LDL lowering
- We disagree with the rationale to not reimburse inclisiran on the basis that "*clinically relevant cardiovascular-related morbidity and mortality outcomes were exploratory outcomes and the trials were not powered to detect statistical significance; hence, the effect of inclisiran on cardiovascular morbidity and mortality has not been determined*" (Page 3 of draft recommendation). The primary goal in treating these patients is a reduction in LDL cholesterol, and the relationship between reducing LDL cholesterol and reducing cardiovascular morbidity has been established beyond reasonable doubt(1). Furthermore, the mechanism by which inclisiran acts to increase the expression of LDL receptors by inhibiting PCSK9 has already been shown to reduce cardiovascular morbidity in large clinical trials of other agents that act through this same pathway (*i.e.*, PCSK9 monoclonal antibodies) (2,3). While demonstrating the magnitude of the reduction in cardiovascular morbidity with inclisiran will be important, and will be established by the ongoing ORION-4 trial, we strongly disagree with denying high-risk patients access to this therapy until those results are available (estimated to be in 2027).
- From our perspective as clinical experts in this area, we would recommend using inclisiran to treat high risk patients who require additional LDL lowering prior to the availability of the cardiovascular outcomes trial, given the overwhelming body of evidence establishing a consistent, log-linear relationship between reduction in LDL cholesterol and reductions in the occurrence of major adverse cardiac events(1)
- The rationale to not reimburse inclisiran on the basis above for patients with HeFH is particularly troublesome. No currently used drug (statins, ezetimibe, PCSK9 mAb) has been

shown in a randomized controlled trial to reduce cardiovascular morbidity specifically in patients with HeFH, and it is extremely unlikely that such a trial would ever be conducted due to the logistical challenges of performing a large clinical trial in patients with a rare genetic conduction, as well as the lack of clinical equipoise about the need to aggressively lower LDL cholesterol in these patients. Indeed, most clinical experts would consider it unethical to conduct such a trial. The Committee's rationale therefore sets a bar of evidence that will never be reached for this group of patients, and in so doing would deny them access to much needed new therapies.

- Lastly, we disagree with the Committee's rationale that inclisran not be reimbursed because "*no health-related quality of life (HRQoL) data was included*" (Page 3 of draft recommendation). HRQoL does not appear to be relevant for a medication whose purpose is to treat an asymptomatic risk factor (hypercholesterolemia).

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

If not, what aspects are missing from the draft recommendation?

- While the Committee has summarized the input provided by our group (Page 6 of draft recommendation), it is not apparent how this input was incorporated into the decision making, rationale, or final decision presented on page 3. Given that our input was the only clinician input provided, that it highlighted the need for new therapies to lower LDL in high risk patients, and the promise that inclisiran holds, we would like to see this input specifically incorporated into the Committee's rationale and decision.

- We are also concerned that our input has been misinterpreted as indicating that inclisiran should only be used "depending on the results of currently ongoing CV outcome trials" (page 6 of draft recommendation). As stated above, based on the abundance of evidence demonstrating that reductions in LDL cholesterol lower the risk of cardiovascular events, we would endorse the use of incisiran in appropriate patients prior to the availability of CV outcomes trials. While the completion of the CV outcomes trials is important, the use of inclisiran should not be dependent on those data given the magnitude of the unmet medical need.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒

If not, please provide details regarding the information that requires clarification.

As described above, the rationale that cardiovascular outcome trials would be required to support a recommendation to reimburse a product for patients with HeFH lacks clarity, and is disconnected from the reality of treating these patients as such a trial is extremely unlikely to ever occur.

Secondly, why health-related quality of life data would be relevant to a drug to treat hypercholesterolemia is not apparent and should be clarified.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification. No comments.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification. N/A		

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- 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 feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please 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 declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒

If yes, please list the clinicians who contributed input and whose declarations have not changed:

- Liam Brunham
- GB John Mancini
- Carolyn Taylor
- Christopher Franco
- Peter Tan
- Gordon Hoag
- Gordon Francis
- Michael Chen

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (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.

Conflict of Interest Declaration

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.

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (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.

Conflict of Interest Declaration

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.

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (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.

Conflict of Interest Declaration

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.

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (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.

Conflict of Interest Declaration

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.

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (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.

Conflict of Interest Declaration

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.

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	☐	☐	☐	☐

References

1. Ference BA, Ginsberg HN, Graham I et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2017;38:2459-2472.
2. Sabatine MS, Giugliano RP, Keech AC et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med 2017;376:1713-1722.
3. Schwartz GG, Steg PG, Szarek M et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. New England Journal of Medicine 2018;379:2097-2107.

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	
Brand name (generic)	Leqvio (Inclisiran)
Indication(s)	Dyslipidemia
Organization	Atlantic Cardiovascular Society
Contact information[a]	Name: Dr Ronald Bourgeois

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒
Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale. See comments in 5.		

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒
If not, what aspects are missing from the draft recommendation? See comments in 5.		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification. To the CADTH recommendation panel: I am writing on behalf of the Atlantic cardiovascular Society (ACS). This is in response to the CADTH recommendation not to list this medication.		

This medication has beneficial effects of lowering LDL cholesterol about 50%

Multiple studies have shown that lowering cholesterol are associated with the reduction in cardiovascular events including stroke, heart attack and death.

Prior approval by this body of PCSK9 inhibitors was done prior to having endpoint data for these medicines.

If the reason for not listing is price, it is my understanding that this may be adjusted when negotiating with the provinces. Price alone should not be a reason to give a negative response to this medication.

For your information, in the UK, the NICE has given a favourable recommendation and Novartis has provided the drug at a substantially reduced cost.

It would be most appropriate to have Inclisiran listed to be available for patients, to substantially lower LDL cholesterol, and eventually potentially reduce the risk of cardiovascular events such as heart attack, stroke, and death. Studies looking into these endpoints are ongoing.

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- 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.
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- For conflict of interest declarations:
  - Please 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.
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  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☒
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Dr Ronald Bourgeois*
Position	*President , Atlantic Cardiovascular Society*
Date	*Please add the date form was completed (22-09-2021)*
☒	**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	

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.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Nil	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (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.

Conflict of Interest Declaration

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.

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (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.

Conflict of Interest Declaration

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.

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 4

Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (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.

Conflict of Interest Declaration

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.

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 5

Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (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.

Conflict of Interest Declaration

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.

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	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	
Brand name (generic)	Leqvio (inclisiran)
Indication(s)	Primary hypercholesterolemia
Organization	Division of Cardiology, University Ottawa Heart Institute
Contact information[a]	Name: Ruth McPherson, MD, PhD, FRCPC

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒
Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale. ***Please read attached document***		
Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☐
If not, what aspects are missing from the draft recommendation? ***N/A Univ Ottawa Heart Institute was not invited to provide input***		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification. ***Please see comments in attached document. Unclear why committee agreed that agents that lower LDL-C reduce ASCVD risk but failed to approve inclisiran.***		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification. ***Lack of attention to the need for inclisiran in the treatment of high risk ASCVD patients***		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification. *N/A*		

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- 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.
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- For conflict of interest declarations:
  - Please 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 declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☒
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Ruth McPherson, MD, PhD, FRCPC*
Position	*Prof Medicine, Director Lipid Clinic, Division Cardiology, Univ Ottawa Heart Institute*
Date	*Please add the date form was completed (22-09-2021)*
☒	**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	

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.				
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 Canada	☒	☐	☐	☐
HLS Therapeutics	☒	☐	☐	☐
Novartis	☒	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Robert Beanlands, MD, FRCPC*
Position	*Chief of the Division of Cardiology, University of Ottawa Heart Institute*
Date	*Please add the date form was completed (22-09-2021)*
☒	**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				
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.				
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	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Marino Labinaz, MD, FRCPC*
Position	*Cardiologist, University of Ottawa Heart Institute*
Date	*Please add the date form was completed (22-09-2021)*
☒	**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				
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.				
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	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Lyall Higginson, MD, FRCPC*
Position	*Cardiologist, University of Ottawa Heart Institute*
Date	*Please add the date form was completed (22-09-2021)*
☒	**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

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.

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Renee Hessian, MD, FRCPC*
Position	*Cardiologist, University of Ottawa Heart Institute*
Date	*Please add the date form was completed (22-09-2021)*
☒	**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

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.

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	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0681-000
Brand name (generic)	Inclisiran (Leqvio)
Indication(s)	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 (nFH) with atherosclerotic cardiovascular disease (ASCVD)
Organization	Canadian Cardiovascular Society
Contact information[a]	Name: Kendra Pelland, Program Manager, Policy & Advocacy

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation?	Yes	☒
	No	☐

The Canadian Cardiovascular Society (CCS) strives to ensure the Canadian cardiovascular community of physicians and health care providers have access to and are providing optimal treatments for patients to reduce their cardiovascular risk on the basis of the current clinical evidence. To this end, the CCS has recently published updated guidelines (2021 CCS Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults Published: March 26, 2021 DOI: https://doi.org/10.1016/j.cjca.2021.03.016) which are an objective, nonbiased document created by experts on the basis of the best available evidence to allow clinicians physicians and patients to make collaborative treatment decisions in this therapeutic arena. At the time of the development and journal peer-review of the dyslipidemia guideline, inclisiran had yet to receive its Notice of Compliance (NOC) from Health Canada. While the CCS did not make recommendations regarding the use of this agent in this guideline, we did provide brief commentary related to its potential within the document:

"*Inclisiran is an experimental small interfering RNA molecule that inhibits the translation of PCSK9. In the phase III Trial to Evaluate the Effect of Inclisiran Treatment on Low Density Lipoprotein Cholesterol in Subjects With Heterozygous Familial Hypercholesterolemia (ORION-9), Inclisiran for Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-density Lipoprotein Cholesterol (ORION-10), and Inclisiran for Subjects With ASCVD or ASCVD-Risk Equivalents and Elevated Low-density Lipoprotein Cholesterol (ORION-11) trials, inclisiran showed LDL-C lowering in patients with heterozygous FH or with, or at high risk of, atherosclerotic CVD. The ongoing phase III A Randomized Trial Assessing the Effects of Inclisiran on Clinical Outcomes Among People With Cardiovascular Disease (ORION-4) is evaluating whether this LDL-C reduction with inclisiran translates to a reduction in MACE among patients with CVD.*"

The CADTH review identified that "clinically relevant cardiovascular morbidity and mortality outcomes were exploratory outcomes in the trials (ORION-9, ORION-10 and ORION-11) and the trials were not powered to detect statistical significance" which led them to conclude that the effect of inclisiran on cardiovascular morbidity and mortality has yet to be determined for patients with HeFH or nFH with ASCVD. As Canada's national, professional association that represents a cardiovascular community

of physicians, researchers, specialist pharmacists, trainees and allied health professionals who are united by a dedication to elevate, educate and advocate for the heart health of all Canadians we are eagerly anticipating the cardiovascular outcome results from the ORION-4 trial, as well as the long-term safety and efficacy data from the open label long-term extension study (ORION-8).

CCS recognizes that inclisiran represents a novel therapeutic class of agents -- small interfering RNA (siRNA) molecules. In this case, it is a molecule that reduces the production of PCSK9 through gene silencing. Given the current limited number of siRNA therapeutic agents marketed for any indication, it is not surprising that this novel mechanism of action of inclisiran (compared to the PCSK9-inhibitors marketed) has resulted in CDEC commenting that "this difference in mechanism of action increases the uncertainty around the long-term efficacy and safety." We are hopeful that the long-term safety and efficacy data from the open label long-term extension study (ORION-8) will satisfy this concern.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐

While the CCS was not involved in providing stakeholder input to CADTH for this draft recommendation, we clearly note that CADTH sought input from the following:

(i) One clinical specialist with expertise in diagnosing and treating patients with HeFH and nFH with ASCVD; and

(ii) Input from an informal clinician group, consisting of lipid specialists and physicians working in lipid clinics in British Columbia, including the Healthy Heart Program Prevention Clinic at St. Paul's Hospital, the Surrey Lipid Clinic at Surrey Memorial Hospital, and the Victoria Lipid Clinic.

In reading the clinician input summarized in the draft recommendation document, we feel that these clinicians adequately addressed any comments or insight that we would have provided had the CCS been engaged to provide input to the development of the draft recommendation. The CCS emphasizes that the 2021 CCS dyslipidemia guideline should be utilized to guide the CADTH recommendations for identifying and treating patients (HeFH patients without ASCVD and whose LDL-C is above the threshold of ≥2.5 mmol/L or <50% reduction from baseline despite maximum dose or maximum-tolerated dose statin ± ezetimibe; or nFH patients with ASCVD whose LDL-C is above the threshold of ≥1.8 mmol/L despite maximum dose or maximum-tolerated dose statin ± ezetimibe) with inclisiran to reduce CV risk and improve CV outcomes.

In the future, the CCS hopes that CADTH's Canadian Drug Expert Committee (CDEC) will look to the CCS dyslipidemia guideline for direction in identifying and treating patients with inclisiran, in addition to the clinical evidence from trials. We also hope that CDEC would consider the CCS as an important stakeholder in cardiovascular medicine who is well-positioned to assess and recommend appropriate course of action that will advance the heart health of all Canadians.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

The document clearly articulates the rationale for CDEC's draft recommendation. The discussion points on page 4 clearly articulate the key components that led CDEC to this final decision. While not all clinicians may fully support the controversy contained in all of these discussion points, they provide clear insight on CDEC's perspective. As clinicians, we all want rapid access to new therapies

that have the potential to improve the clinical outcomes for our patients. However, we also recognize that drug development and approval is an in-depth and rigorous process, and that science and clinical evidence must support our enthusiasm to prescribe new medications, especially those with novel mechanisms of action for our patients.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☐
N/A		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
As the current draft recommendation is “Do Not Reimburse” there are no reimbursement conditions to comment on at this time. However, the CCS and its clinician members eagerly anticipate an update and revision to the current recommendation once the cardiovascular outcome trial results are available and/or the long-term safety and efficacy data.		

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- 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 feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please 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 declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☒
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Dr. Glen Pearson*
Position	*Professor of Medicine (Cardiology); Co-Director, Heart Transplant Clinic; Chair, Trainee Research Access Committee (TRAC), Department of Medicine, Division of Cardiology, University of Alberta*
Date	*21-09-2021*
☒	**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				
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.				
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	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Dr. George Thanassoulis*
Position	*Associate Professor - Department of Medicine, Division of Experimental Medicine, McGill University*
Date	*21-09-2021*
☒	**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				
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.				
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	☐	☐	☒	☐
HLS	☐	☐	☒	☐
Novartis	☐	☐	☒	☐

New or Updated Declaration for Clinician 3	
Name	*Dr. Kim Connelly*
Position	*Associate Professor, Cardiovascular Platform, University of Toronto*
Date	*21-09-2021*
☒	**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				
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.				
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	☒	☐	☐	☐
AstraZenaca	☐	☐	☐	☒
Boehringer Ingelheim	☐	☐	☐	☒
Eli Lilly	☐	☐	☐	☒
Merck	☒	☐	☐	☐
Servier	☒	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (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.

Conflict of Interest Declaration

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.

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (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.

Conflict of Interest Declaration

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.

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	☐	☐	☐	☐

Re: https://www.cadth.ca/open-calls-input-and-feedback?brand_name=
Leqvio&generic_name=inclisiran&indications= Primary hypercholesterolemia

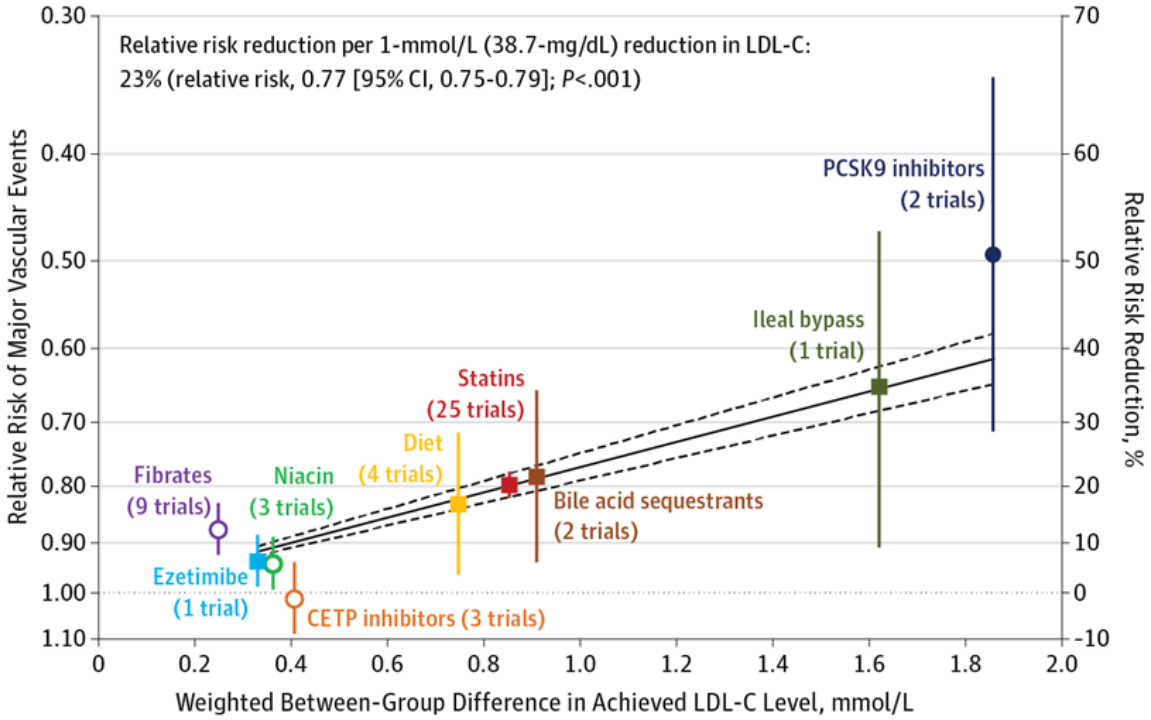
As members of the Division of Cardiology at the University of Ottawa Heart Institute, we wish to express our strong disagreement with the CADTH decision not to reimburse inclisiran (Leqvio™).

- The first listed discussion point underlying this decision was that cardiovascular outcome data are not yet available.

Here we would like to remind the committee that the LDL-C lowering effect of inclisiran is equivalent to that of the *PCSK9 monoclonal antibodies that were approved based on efficacy for LDL-C reduction before CV outcome studies were complete.* We now have clear evidence that agents that target the PCSK9 pathway reduce MACE outcomes in patients with existing ASCVD who are already on statin +/- ezetimibe therapy. Further it is important to note that, in response to addition of a PCSK9 inhibitor, evolocumab, those ASCVD patients with a recent ACS event or a history of recurrent events experienced a 24% and 30% decrease in MACE over a 3-year treatment period with a NNT of 35 and 29 respectively.

The committee should be reminded that LDL-C reduction by agents acting via diverse mechanisms has consistently lowered the incidence of myocardial infarction and stroke to an extent determined by their clinical efficacy.

As illustrated below in a recent publication in JAMA 2016;316:1289-1297.doi:10.1001/jama.2016.13985, the relative reduction in risk for major vascular events is directly related to the magnitude of LDL-C lowering as compared to placebo.



Given these data, there is no reason to believe that inclisiran treatment should not provide similar efficacy in terms of MACE outcomes as compared to other therapies that target PCSK9 and/or reduce LDL-C to a similar extent. Concern was raised that ITC data on the LDL-C reduction by inclisiran was only 24 weeks. Given the dosing schedule, 3mos then q 6mos, one can only conclude that the long-term lowering of LDL-C will be similar or slightly greater.

- As noted in the second discussion point, the RCTs with clinical endpoints for MACE, ORION-4 and VICTORIAN-2-PREVENT are underway.

It would be a disservice to ask high risk ASCVD patients, who would now benefit from addition of inclisiran to their current regimen, to wait until late 2026 when such outcome data will be available.

- The third discussion point queried the tolerability of inclisiran vs available PCSK9 inhibitors

A major advantage of inclisiran is that it is administered q 6 mos rather than q 2wks. There is also no requirement for self-injection or refrigerated storage of pens that are discarded after a single injection. The q 6-month dosing regimen is such that inclisiran can be administered by the patient at home, at a local pharmacy or at the time of a routine 6 month follow-up by the treating physician. In discussions with our patients, including those currently treated with evolocumab or alirocumab, there has been almost unanimous preference for a q 6-month dosing schedule. The tolerability of this agent was demonstrated in ORION-10 and ORION-11, where the most common side effects of inclisiran were injection site reactions occurring in in 3.1% of inclisiran treated patients vs 0.1% in placebo (reviewed in JACC 2021;77:1194-6).

- The fourth and fifth discussion points encompassed “efficacy and safety concerns related to the *novel* mechanism of action of inclisiran”.

Here the committee should be aware that inclisiran is one of a growing number of agents targeting RNA to impede the hepatic synthesis of a specific protein. Others include antisense RNA to *APOCIII* to lower plasma triglycerides and to *ANGPTL3* to reduce both triglycerides and LDL-C. Patisiran (Onpattro™) for the treatment of hereditary transthyretin (hATTR) amyloidosis is already in use.

In terms of safety and specificity, there is no signal for serious adverse events including thrombocytopenia. Here an important modification that applies to inclisiran as well as other agents is its GalNAc conjugation that targets this agent directly to the liver via the asialogycorotein receptor (ASGPR). Inclisiran is delivered in nanoparticles and does not enter the nucleus but resides in the cytoplasm of the hepatocyte where it is protected from RNA degradation for several months.

Inclisiran specifically targets the mRNA template for PCSK9 translation and does not alter the synthesis of other proteins. *While there is no substantial evidence that PCSK9 is required by other cells or tissues, this agent does not alter PCSK9 synthesis in the brain, adipose tissue or elsewhere.*

Although the duration of effect is > 6 months, inclisiran does not have permanent activity.

- Most importantly, many of our highest risk ASCVD patients are not achieving adequate LDL-C control as stipulated by the recent CCS guidelines and despite treatment with a high potency

statin and ezetimibe. *This is reflected in recurrent events that might have been prevented, at enormous personal cost and a burden to our already compromised healthcare delivery system.*

Currently our patients with aggressive ASCVD are not eligible for government funding for a PCSK9 inhibitor, unless they have *bona fide* familial hypercholesterolemia, and many do not have private insurance. Although consideration of price is not a mandate of CADTH, it is known that inclisiran will be less expensive that current PCSK9 therapies and it is anticipated that cost will be substantially lower for government payers.

Here, we wish to make CADTH aware of the recent announcement from the United Kingdom:

"NICE has today (1 September 2021) issued draft final guidance recommending the novel anti-cholesterol drug inclisiran (Leqvio and made by Novartis) for people with primary hypercholesterolaemia or mixed dyslipidaemia who have already had a cardiovascular event such as a heart attack or stroke."

As noted by Meindert Boysen, NICE deputy chief executive and director of the Centre for Health Technology Evaluation ***"Inclisiran represents a potential game-changer in preventing thousands of people from dying prematurely from heart attacks and strokes."***

HEART HEALTH INSTITUTE

CARDIAC IMAGING
Dr. Vineeta Ahooja
Dr. Lauren Tobe
Dr. Raymond Yan
Dr. Kibar Yared

DIAGNOSTIC CATH
Dr. Sanjay Dhingra
Dr. Amir Janmohamed
Dr. James Swan

INTERVENTIONAL CARDIOLOGY
Dr. Jason M. Burstein
Dr. Peter Gladstone
Dr. Ram Vijayaraghavan

HEART RHYTHM CLINIC
Dr. Amir Janmohamed
Dr. Bhavanesh Makanjee
Dr. Derek Yung

September 23, 2021

To CADTH/ CDEC

I am writing in response to your recent draft recommendation for Inclisiran. In this draft the Canadian Drug Expert Committee (CDEC) recommended that Inclisiran should not be reimbursed to further reduce LDL C levels in adults with HeFH or non-familial hypercholesterolemia (nFH) with ASCVD who are on maximally tolerated dose of a statin, with or without other LDL-C lowering therapies.

One of the main reasons provided was insufficient evidence to evaluate the clinical benefit of inclisiran in patients with HeFH or nFH with ASCVD

I would like to speak to this.

The antibody mediated PCSK9 inhibitors, evolocumab and alirocumab have been studied in trials of duration roughly 2 years. We do have a longer duration of follow-up as well real world evidence that tells us that the relative risk reduction seen with these 2 agents in patients with established cardiovascular disease and elevated LDL-C mimic those relative risk reduction as there is seen in the many statin trials.

We now evidence for CV protection and reduction in secondary cardiovascular events with several agents, all of which operate by upregulating the LDL receptor.

1. Statins: by a mechanism mediated by inhibition of HMG Co-A reductase, lead to an upper regulation of LDL receptors and thereby decrease in LDL cholesterol.

2. Ezetimibe is a potent and selective inhibitor of cholesterol absorption which has been shown to reduce the overall delivery of cholesterol to the liver thereby promoting the synthesis of LDL receptors with a subsequent reduction in serum LDL C

3. PCSK9inhibitors: Through an antibody mediated mechanism break down the PCSK9 molecule thereby preventing breakdown of the LDL receptor leading to an upper regulation of LDL receptors and again a reduction in serum LDL C

Inclisiran would be a fourth class of drugs with the same effect, upregulation of LDL receptor and reduction in serum LDL-C. As it has a longer half life, patients would have the distinct advantage of a decrease frequency of administration and longterm suppression of LDL-C.

[redacted]

As we know LDL-C is causal in atherosclerosis and this has been seen in many studies. Early and longterm suppression of LDL-C leads to a significant reduction in morbidity and mortality by reducing major adverse cardiovascular events.

I hope that you will find this information helpful in further decision making regarding this novel therapeutic agent.

Warm regards,

Vineeta Ahooja MD FACC FASE

Advanced Cardiac Imaging, Cardiovascular Medicine

[redacted]

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0681-000
Brand name (generic)	INCLISIRIN
Indication(s)	ASCVD & ELEVATED LDL-C
Organization	KAWARTHA CARDIOLOGY CLINIC
Contact information[a]	Name: MICHAEL HARTLEIB

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒
Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.		

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒
If not, what aspects are missing from the draft recommendation?		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- 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 feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please 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 declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☑
	Yes	☐
If yes, please detail the help and who provided it.		
3. Did you receive help from outside your clincian group to collect or analyze any information used in this submission?	No	☑
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*DR.MICHAEL HARTLEIB*
Position	*CHIEF / CARDIOLOGIST*
Date	*23/09/2021*
☒	**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	

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.

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	☐	☐	☐	☐

*MAY BE INVOLVED IN WORKING CLINICAL TRIALS

New or Updated Declaration for Clinician 2	
Name	*DR. WILLIAM HUGHES*
Position	*CARDIOLOGIST*
Date	*23/09/2021*
☒	**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

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.

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*DR. KATIE DOUCET*
Position	*CARDIOLOGIST*
Date	*23/09/2021*
☒	**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

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.

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*DR. KAREN WAGNER*
Position	*CARDIOLOGIST*
Date	*23/09/2021*
☒	**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

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.

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*DR. JOHN REESOR*
Position	*CARDIOLOGIST*
Date	*23/09/2021*
☒	**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

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.

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 6	
Name	*DR. PAUL SANDHU*
Position	*CARDIOLOGIST*
Date	*23/09/2021*
☒	**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

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.

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	
Position	
Date	
☐	**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

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.

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	☐	☐	☐	☐

Michael C. Hartleib, MD, FRCPC

CARDIOLOGIST

Michael C. Hartleib Medicine Professional Corporation

THE KAWARTHA CARDIOLOGY CLINIC

[redacted]

[redacted]

To Whom It May Concern:

RE CADTH Inclisirin Reimbusement Recommendation (Draft)

This document reflects the collected responses and opinions of the physicians identified herein.

We disagree with the recommendation that inclisiran should not be reimbursed. We believe strongly that inclisiran should be made available to physicians and patients in Canada as an adjunct to diet and lifestyle to further lower LDL-C in high-risk patients.

In terms of the efficacy of inclisiran the committee rightly identifies that long term outcome studies are pending however we are more convinced by the demonstrated safety and efficacy of inclisiran in lowering LDL-C. It has been clearly established that LDL-C lowering via upregulation of LDL receptor expression leads to substantial risk reduction, and that risk reduction is independent of the mechanism of LDL receptor upregulation. This has been clearly 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. Accordingly, the demonstrated safety and efficacy of inclisiran in sustained lowering of LDL, in our opinion, is sufficient to warrant availability of another important tool in the armamentarium of vascular risk reduction.

As has been identified many patients are completely or partially intolerant of currently available lipid lowering strategies. In addition, many patients struggle with adherence. We are clinicians with substantial 'boots on the ground' experience treating vascular patients and we can confirm that non-adherence (either intentional or un-intentional) is a very significant clinical challenge and increases patient risk.[3] 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. We can envisage a future whereby the clinician-patient relationship is strengthened by our ability to provide this therapy in the office during patient visits. We have been looking forward to the opportunity to provide a therapy to patients that

provides significant and sustained LDL-C lowering with both ease of use and which resolves concerns associated with adherence.

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 informed by 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.

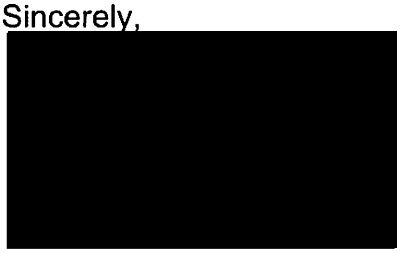
With the above in mind, we formally request that the committee reconsider their decision such that this unique and necessary therapy can be made available to busy clinicians and high-risk patients.

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.

Sincerely,



Michael C Hartleib, MD, MSc, FRCPC
Chief and Director of Medicine, Peterborough Regional Health Centre
Director, Kawartha Cardiology Clinical Trials

On Behalf of:

Dr. William Hughes

Dr. Katie Doucet

Dr. Karen Wagner

Dr. John Reesor

Dr. Paul Sandhu

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0681
Brand name (generic)	Leqvio (inclisiran)
Indication(s)	Primary hypercholesterolemia
Organization	Corcare Inc
Contact information[a]	Name: Joseph Ricci MD FRCP [redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

The committee's recommendations were diligent and thoughtful We respectively disagree with the lack of approval. On balance, we believe that in the current scientific and health system context the evidence supports approval of the medication.

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***

Recommendation: Do Not Reimburse

i. ***The judgement states that "clinically relevant cardiovascular-related morbidity and mortality outcomes were exploratory outcomes and the trials were not powered to detect statistical significance; hence, the effect of inclisiran on cardiovascular morbidity and mortality has not been determined"***

This justification is factually correct but lacks scientific and health system context.

The agent lowers LDL in these clinical groups efficiently. The reduction of LDL has been shown to correlate with patients' outcomes in familial hyperlipidemia and established vascular disease. At this time, the current Canadian Guidelines identify LDL as predictor of negative outcome and modified the current management paradigm to focus on LDL thresholds for therapy in the statin indicated patient. The concept of treating to a specific target has been replaced by the concept that lower LDL cholesterol is a desirable to improve outcomes.

The agent has the potential to be more effective than current options. The agent is delivered on a most practical with infrequent dosing contributing to improved compliance and lower achieved population LDL levels. This advantage is significant and high value in the context of persistent large system related factors that cause substantial underutilization of available therapies with excess population morbidity and mortality.

ii. ***The judgement further states that ' Direct comparative evidence for inclisiran versus proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (evolocumab and alirocumab) or other add-on agents such as ezetimibe was not identified. One sponsor-submitted indirect***

treatment comparison (ITC) suggested that inclisiran does not have a consistent nor distinct difference in efficacy in LDL-C reduction when compared to evolocumab or alirocumab"

This justification is factually correct but is a factor that should not be relevant in this specific application.

The rational would more applicable to pharmacology within the same class that do not have novel attributes. This the agent utilizes a novel pharmacologic mechanism to achieve long-term PSK9 inhibition. The agent does not share molecular or pharmacologic properties with the preceding classes of medications.

iii. ***the sponsor submitted ITC used study results collected after 24 weeks of treatment which is a relatively short duration compared in a chronic condition, like hypercholesterolemia.***

This statement is factually correct but ignores the context of the finding.

As per i) the level of LDL lower is a substantial finding and a proven marker of outcome. There is evidence that the LDL is durable and the duration of study is not insufficient to justify exclusion in context of the current guidelines related to LDL lowering in established cardiovascular disease.

iv. ***CDEC noted that there are two ongoing studies (ORION-4 and ORION-8) which are expected to provide further evidence to better characterize the efficacy and safety of inclisiran in preventing pertinent clinical outcomes, including the reduction of cardiovascular events and cardiovascular related death, as well as provide long-term efficacy and safety data for inclisiran.***

This is factually correct but lack context to the other findings and current Canadian Guidelines.

The timelines to completion and approval on this basis are unnecessary and would excessively delay implementation in the context of the arguments (i-iiii) and deprive the health care system of an effective management option for an unreasonable period of time.

v. ***CDEC discussed that there is no evidence that inclisiran will be better tolerated in patients who did not respond or were intolerant to PSCK9 inhibitors and that the efficacy of switching from PCSK9 inhibitors to inclisiran on reduction in LDL-C levels, cardiovascular morbidity and mortality remains uncertain.***

This justification lacks context and is not factually defesible and ignores recent data relating to the genesis of intolerance

The comparator drugs are well tolerated in absolute terms and relevant to other therapies. Equivalency is not a negative outcome where the comparator is well tolerated.

Moreover, the "Sampson" trial confirmed that over 90% of imputed side effects with oral therapies relate to the act of taking pill not the pharmacologic agent; a negative outcome that would not occur in an infrequent dosing parenteral agent and were the most frequent side effect was local not systemic

vi. ***CDEC stated that "Given that hypercholesterolemia requires lifelong treatment, CDEC discussed that there is uncertainty regarding the long-term efficacy and safety of inclisiran***

over currently available PCSK9 inhibitors (evolocumab and alirocumab) for the treatment of HeFH or nFH with ASCVD."

This is a standard has not applied to prior agents for this segment at first approval for use and lacks context with respect to the long-term impact of LDL lowering (see i-iii).

In the early assessment of statins long term outcome data was a necessary prerequisite for a cardiovascular prevention approval. In the current context confirming the value of LDL lowering, persistence of LDL lowering is sufficient.

We are not arguing in favour of surrogate measures for approval. The lowering of LDL in the context of the current guidelines is not a surrogate for outcomes or efficacy. There is sufficient evidence that it is a mediator of outcomes and where reduced outcomes are reliably and predictably improved.

vii. ***CDEC states that " Inclisiran has a novel mechanism of action that is different from currently available PCSK9 inhibitors. CDEC discussed that this difference in mechanism of action increases the uncertainty around the long-term efficacy and safety.***

The novel mechanism and long duration of action are factually correct but are inconsistent with prior statements and have no clear relevance to the approval.

The "novel mechanism" statement is contradictory to prior statements that the agents were not novel relative to PSK9i.

It is reasonable to address long term safety concerns are different for drugs with long and irreversible mechanisms of action. However, this agent has a long but finite activity and there is no evidence to support this concern during the 6-12 month period of time where drug activity is measurable. It is not reasonable to attribute potential risk beyond the period of the drug action without a signal for risk or mechanistic hypothesis for a concern.

We appreciate the opportunity to present our thoughts on this important issue. It would be our pleasure to contribute in future in any manner of value to the process

Corcare Inc.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒
Corcare was not an invited participant and did not make a submission		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
	Yes	☒

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	yes	☒
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clincian group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☒
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Joseph Ricci MD FRCPC*
Position	*Director Corcare Inc*
Date	*20-10-20121*
☒	**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

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.

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Nisha D'Mello*
Position	*Director Corcare Inc*
Date	*20-10-2021*

☒	**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

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.

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

New or Updated Declaration for Clinician 3	
Name	*Paul Galiwango*
Position	*Director Corcare Inc*
Date	*20-10-20121*
☒	**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

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.

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Ashok Mukherjee*
Position	CEO, Corcare Inc
Date	*20-10-20121*
☒	**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

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.

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Saleem Kassam*
Position	*Director Corcare*
Date	*20-10-20121*
☒	**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

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.

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	☐	☐	☐	☐

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0681
Name of the drug and Indication(s)	Inclisiran (Leqvio) 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
Organization Providing Feedback	FWG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	☐
	No requested revisions	X

2. Change in recommendation category or conditions
Complete this section if major or minor revisions are requested

N/A

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
N/A
b) Reimbursement conditions and related reasons
N/A
c) Implementation guidance
N/A

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0681
Brand name (generic)	Leqvio (inclisiran)
Indication(s)	HeFH and nFH ASCVD not managed on maximally tolerated statin dose
Organization	Canadian Heart Patient Alliance
Contact information[a]	Name: Durhane Wong-Rieger [redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

The Canadian Heart Patient Alliance strongly disagrees with the draft recommendation of CDEC. The report acknowledged that inclisiran was proven to be statistically significant in lowering LDL-C against placebo but chose not to recommend reimbursement because there were no clinically relevant cardiovascular morbidity or mortality outcomes. This recommendation is dismaying not only because patients nonresponsive to current therapies will be denied a treatment with proven benefits but also because the rationale offered is untenable given the current state of knowledge about the correlation between lowering LDL-C and reduction in CV events. We offer just one recent study (Kidney Int. 2018 Apr; 93(4): 1000–1007) which states: "Prospective studies have also shown that low-density lipoprotein cholesterol (LDL-C) is positively associated with risk of major vascular events,[7, 8] while randomized trials of statins[9] (and, more recently, of proprotein convertase subtilisin/kexin type 9 or PCSK-9 inhibitors[10]) have shown that lowering LDL-C reduces cardiovascular risk, confirming that LDL-C is a cause of atherosclerotic disease." [We have left the secondary references in the quote.]

Moreover, we object to the CDEC attempting to justify their denial by citing the patient input as indicating the need for treatment that reduces CV morbidity and mortality. As patients suffering from uncontrolled LDL-C and experiencing a variety of serious cardiovascular events, including death, we understand and believe the link between lowering LDL-C and reducing CV events. For patients with diabetes, it is accepted that lower blood glucose levels to target will reduce symptoms such as fatigue but also complications such as kidney disease, nerve damage, heart problems, eye problems, and stomach problems. We would not expect that new insulin therapies would need to demonstrate reduction in these serious outcomes in addition to managing blood glucose levels.

We provided input to the initial assessments for PCSK9s, which CADTH recommended for reimbursement in 2016. We recognize that CADTH was looking for CV events outcomes at that time but their positive recommendation was made with acknowledgement that there were research gaps resulting in "insufficient evidence" as noted:

- *The product monograph states effect of evolocumab on CV morbidity and mortality not determined*
- *Long-term safety and efficacy requires further evaluation*

In that case, as is now, there was expectation of long-term, confirmatory evidence from additional studies but reimbursement was not denied pending extended studies. Given our much more

extensive knowledge about the reduction in CV events with successful lowering of LDL-C with alternative therapies for patients unsuccessful on statins with and without ezetimibe.

Moreover, when the manufacturer (of evolocumab) provided extended study outcomes, they were able to demonstrate impact only on "key secondary composite of CV death, MI, and stroke" but could not demonstrate a statistically significant benefit over placebo for overall mortality or for CV mortality. Given the success with PCSK9s, we would have expected CDEC to be able to extrapolate from those studies and real-world evidence to reimburse another statin alternative that was effective in safely lowering LDL-C.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

If not, what aspects are missing from the draft recommendation?

The CHPA does not feel that CADTH considered our stakeholder input. While there was a representative summary included, we do not feel that the recommendation reflected the feedback from our patient community. We were particularly distressed by the conclusion that because there had been no HRQoL data submitted, the impact on quality of life was unknown. This finding overlooked, ignored, or discounted the voluminous, detailed, and compelling patient testimonies on the impact of current treatments on quality of life. Specifically, we reported that 20% experienced on-going challenging managing their cholesterol levels, with detailed descriptions of inability to tolerate statins, inability to get cholesterol to target despite maximum statin dosing plus supplemental medicines, pain and other adverse effects to statins, and inability to tolerate or manage with PCSK9s.

We were also puzzled and disconcerted by the reference to the lack of evidence of benefits of switching from PCSK9 to inclisiran. The patients were not expecting switch for patients who were responding to PCSK9s or were well managed on their current statin regimen.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☒

If not, please provide details regarding the information that requires clarification.

The reasons provided are understandable but the rationale behind them are absolutely not clear; we feel the reasons provided are misguided and inappropriate, based on science and public good sense.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒

If not, please provide details regarding the information that requires clarification.

CDEC seems to fear that inclisiran would not be adequately managed, that is, the implementation guidelines would not be able to restrict prescribing only to those patients with clear evidence of inadequate management on their current treatments or severe adverse effects to statins or PCSK9s.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐

If not, please provide details regarding the information that requires clarification.

Not applicable. Would be good to have specific conditions for prescribing.

[a] CADTH may contact this person if comments require clarification.

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0681-000
Brand name (generic)	inclisiran
Indication(s)	Leqvio 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:
Organization	HeartLife
Contact information[a]	Name: Marc Bains

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

The patient input provided by HeartLife seems to have been taken out of context by CDEC in their recommendation to NOT reimburse inclisiran — while the goal of therapy is to reduce cardiovascular events as the result of therapeutic interventions, it appears that the CADTH Reviewer and the CDEC committee issuing the 'Do Not Reimburse' recommendation does not accept the concept of addressing excessive LDL-C levels to reduce CVD risk.

The DRAFT CADTH report included a comment that CDEC wanted to see evidence that lowering LDL-Cholesterol with inclisiran had an impact on cardiovascular events. It has been understood for decades that lowering LDL-C impacts CV events.

The comment from the Clinical Expert consulted by CADTH (included on page 6 of the recommendation): **"...noted that *LDL-C*, ApoB, and non-HDL-C are guideline recommended biomarkers for CV outcomes."**

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

If not, what aspects are missing from the draft recommendation?

We included in our submission a comment relating to the fact that patients wanted a more convenient dosing schedule (twice a year injection) and fewer adverse events with medications taken for excessive LDL-C — it

appears that this benefit of inclisiran was ***missed*** in the in the CADTH DRAFT recommendation to deny public reimbursement this product in Canada.		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☒
If not, please provide details regarding the information that requires clarification. Yes and no - Need a lay terms document for patient groups and public. A bigger issue within Cadth that should be addressed for all documentation.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- 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 feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Marc Bains*
Position	*Co-Founder*
Date	*Please add the date form was completed (DD-MM-YYYY) 20-09-2021*
☐	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.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

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.

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	☐	☐	☐	☐