CADTH

CADTH REIMBURSEMENT REVIEW

Clinician Input

LEQVIO (inclisiran)

(Novartis Pharmaceuticals Canada Inc.)

Indication: Primary hypercholesterolemia

April 9, 2021

CADTH Reimbursement Review
Clinician Group Input Template

CADTH Project Number	**SR0681-000**
Generic Drug Name (Brand Name)	**Inclisiran**
Indication	Inclisiran is indicated in adults with primary hypercholesterolemia (heterozygous familial and non-familial), as an adjunct to diet: • in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach low density lipoprotein cholesterol (LDL-C) goals with the tolerated dose of a statin or, • alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.
Name of the Clinician Group	**BC Lipid specialists**
Author of the Submission	**Liam Brunham**
Contact information	Name: Liam Brunham Title: Medical Lead, Healthy Heart Program Prevention clinic, St. Paul's Hosp., Associate Professor, University of British Columbia Email: [redacted] Phone: [redacted]

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

This is an informal group consisting of the lipid specialists and physicians working in lipid clinics in British Columbia, including the Healthy Heart Program Prevention clinic at St. Paul's Hospital, the Surrey Lipid Clinic at Surrey Memorial Hospital, and the Victoria Lipid Clinic. Our group frequently communicates to share best practices, collaborates on research and educational projects and meets through various forums including advisory board, conferences, CME and other events.

2. Information Gathering

Please describe how you gathered the information included in the submission.

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

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

Currently Health Canada-approved treatments include statins, ezetimibe and PCSK9 monoclonal antibodies, in addition to dietary therapy consisting of reducing saturated fat intake and dietary cholesterol. All of these therapies are routinely used in clinical practice and endorsed in the 2020 Canadian Cardiovascular Society dyslipidemia guidelines. Other medications such as fibrates are not indicated for LDL-C lowering and do not reduce CV risk. Bile acid resins are seldom used due to poor tolerance and poor LDL-C lowering properties and little evidence for CV risk reduction is available.

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Examples: Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Response:

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

5. Treatment gaps (unmet needs)

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

Examples:

- *Not all patients respond to available treatments*
- *Patients become refractory to current treatment options*
- *No treatments are available to reverse the course of disease*
- *No treatments are available to address key outcomes*
- *Treatments are needed that are better tolerated*
- *Treatment are needed to improve compliance*
- *Formulations are needed to improve convenience*

Response:

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

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

Would these patients be considered a subpopulation or niche population?

Describe characteristics of this patient population.

Would the drug under review address the unmet need in this patient population?

Response:

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

6. Place in therapy

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

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Response:

The drug under review works by inhibiting PCSK9 synthesis, thereby diminishing liver excretion into the circulation and subsequently increasing the expression of hepatic LDL receptors. Thus, inclisiran ultimately works through a common mechanism with other approved lipid lowering therapy with proven ability to lower CV risk safely. It would be the first siRNA drug in class. It would be most likely used as an

add-on to maximally tolerated doses of statins (and/or ezetimibe) in patients who require additional lipid lowering.

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

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

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

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

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

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

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

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

Which patients are most in need of an intervention?

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

Response:

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

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

Examples: *Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)*

Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

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

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

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

For patients with FH specifically, there is a large degree of underdiagnosis, with only ~15% of patients with this condition identified in Canada. There is an ongoing need to improve the identification of patients with FH.

Patients who are asymptomatic should be treated in specific circumstances: 1) patients with FH, 2) patients with documented atherosclerotic disease who have not yet had a clinical event and other guideline-recommended patient groups considered to have high CV risk amenable to the benefits of LDL-C lowering (e.g. high Framingham Risk Patients, patients with DM and patients with chronic kidney disease).

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

Response:

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

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

If so, how would these patients be identified?

Response:

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

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

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

Response:

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

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

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*
- *Stabilization (no deterioration) of symptoms*

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Response:

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

6.10. How often should treatment response be assessed?

Response:

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

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

Examples:

- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

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

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

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

Response:

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

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

If so, which specialties would be relevant?

Response:

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

7. Additional information

7.1. Is there any additional information you feel is pertinent to this review?
Response: Click here to enter response.

8. Conflict of Interest Declarations

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

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

No.

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

No.

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

Declaration for Clinician 1

Clinician Information	
Name	*Liam Brunham*
Position	*Associate Professor, UBC; Medical Lead, Healthy Heart Program Prevention Clinic, St. Paul's Hospital*
Date	*03/27/2021*
☒	**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	
Company	**Check Appropriate Dollar Range**

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

Declaration for Clinician 2

Clinician Information	
Name	*G B John Mancini*
Position	*UBC Professor, Director, CardioRisk Clinic (Vancouver Hospital), Staff Physician Healthy Heart Program Prevention Clinic (St. Paul's Hospital)*
Date	*03/27/2021*
☒	**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				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Amgen	☐	☒	☐	☐
Sanofi	☐	☒	☐	☐
Novartis	☒	☐	☐	☐
HLS Therapeutics	☐	☒	☐	☐
Esperion	☒	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*Carolyn Margaret Taylor*
Position	*Associate Professor, UBC, Medical Director, Cardiac Rehabilitation Program, St Paul's Hospital*
Date	*06/04/2021*
☒	**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				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Amgen	☒	☐	☐	☐
Novartis	☒	☐	☐	☐
Sanofi	☒	☐	☐	☐

Astra Zeneca	x			

Declaration for Clinician 4

Clinician Information	
Name	*Christopher Franco*
Position	*UBC Clinical Assistant Professor, Medical Lead CCU, Staff Cardiologist Royal Jubilee Hospital, Victoria BC*
Date	*07-04-2021*
☒	**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

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

Declaration for Clinician 5

Clinician Information	
Name	*Peter Tan*
Position	*Clinical Assistant Professor (UBC). Cardiologist Surrey Memorial Hospital. Consultant Lipid Clinic, Jim Pattison Outpatient Care and Surgery Centre*
Date	*08-04-2021*
☒	**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

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

Declaration for Clinician 6

Clinician Information	
Name	*Gordon Hoag*
Position	*UBC Professor, Division Head Medical Biochemistry, VIHA, Director and Staff Lipidologist, Victoria Lipid Clinic, Victoria, BC*
Date	*Please add the date form was completed 08-04-2021*

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

Declaration for Clinician 7

Clinician Information	
Name	*Gordon Francis*
Position	*Professor of Medicine, University of British Columbia; Physician, Healthy Heart Program Prevention Clinic, St. Paul's Hospital, Vancouver, BC*
Date	*08-04-2021*
☒	**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				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
N/A	☐	☐	☐	☐

Declaration for Clinician 9

Clinician Information	
Name	*Michael Chen*
Position	*UBC Clinical Assistant Professor, Consulting physician, Victoria Lipid Clinic, Victoria BC*
Date	*06-04-2021*
☒	**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				
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	☒	☐	☐	☐