MEMORANDUM TO: Megan Ashlee Bowes
Vice-President, Corporate Services
CADTH

FROM: Diane McArthur
Chair, Procedural Review Panel

Date: June 13, 2022

RE: Procedural Review of Inclisiran (Leqvio™)

Dear Ms. Bowes,

I am writing on behalf of the Procedural Review Panel (Panel) regarding the results of our recent review of procedures followed by the CADTH/CDEC in its review of Inclisiran (Leqvio™). As you are aware, the Panel's mandate is restricted to determining if there were any procedural errors made by CADTH in its review i.e., did it follow the processes as outlined in the "Reimbursement Review Procedures (December 2021 version) and is not related to the content or scientific issue in the final recommendation.

The Panel has determined that there was no breach of procedures, however while not within its mandate to review the content of the reviews, the Panel strongly recommends that the CDEC/CADTH be more clear in its decision documents. This is especially important during reconsiderations, or where recommendations differ from those made on recently reviewed similar products. Including information about how CDEC has considered input specific to the drug in question as part of each report will enhance stakeholder confidence in the review processes.

The Panel very much appreciated the quality and thoughtfulness of the materials presented by both Novartis and CADTH. The issues brought forward were complex and required much deliberation by the Panel.

The Panel met on Thursday, May 19, 2022 to hear presentations by representatives of Novartis, the manufacturer of Inclisiran (Leqvio™) and the CADTH Drug Review team. The Panel had previously received and reviewed the following documentation:

1. Meeting agenda
2. Procedural Review Application
3. Novartis supporting documentation 1
4. Novartis supporting documentation 2
5. Slide deck (prepared by Novartis)
6. Slide deck (prepared by CADTH)
7. Reimbursement Review Procedures (December 2021 version)
8. CADTH Final Recommendation and Reports: inclisiran | CADTH

Discussion of Key Points

1. Consistency in Drug Reviews

Central to the determination of the Panel was the discussion of "consistency" as it pertained to the objectives of CADTH's mandate which then framed the determination of whether or not there was an error in the application of the Reimbursement Review Procedures.

Novartis proposed that the essential issue before the Panel is whether CADTH lived up to both the "what" and the "how" of application of its procedures. Novartis raised 5 issues of procedural variance.

The Panel found that the first of the proposed issues was the most significant and, depending on the Panel's finding, would provide essential context for its analysis of the remaining issues.

Novartis' initial proposal is that CADTHs procedural objective of "enhancing consistency of drug reviews" should be read to mean that similar products should be reviewed using similar evidentiary standards, and that in its review of Inclisiran (Leqvio™) the CDEC used different standards from those used for two previously reviewed drugs without providing a clear justification for breaching both the "what" and the "how" of the procedures.

CADTH proposed that the phrase "enhancing consistency of drug reviews" should be interpreted in the context of its pan-Canadian role which is to enhance consistency of reviews across provincial and territorial jurisdictions, and that the scientific review of each drug is independent of any product that preceded or was anticipated to follow it through the process. At the request of the Panel, following the meeting CADTH provided a summary of the use of "consistent" and "consistency" throughout the Procedural document, including information from "An Inside Look at the Early History of the CADTH Common Drug Review in Canada" to support this view.

The Panel had a robust discussion on this issue especially in light of its mandate to review procedural issues and not re-examine the scientific issues. The Panel ultimately decided by a vote of 2-1 that CDEC's recommendation on Inclisiran (Leqvio™) did not violate the intent of 'consistency of drug reviews' as cited in CADTH's Reimbursement Review Procedures; therefore, a procedural error relevant to consistency did not occur. The dissenting member of the panel felt that because the CDEC was not clear on the factor(s) that resulted in a negative recommendation for a drug that appears *prima facie* similar in efficacy and safety to two others that received a positive recommendation, the CDEC had committed a procedural error. It would be beyond the mandate of the Panel to review the detailed bodies of information provided to CDEC and comment on the validity of CDEC's recommendation. However, the Panel unanimously recommends that the CDEC should be more explicit in its reports about which factors lead to a differing recommendation for similar drug products. This is particularly important if the products are reviewed in relatively close proximity.

2. Sufficiency of Clinical Expertise

On the second issue, that insufficient clinical experts were involved in the review, the Panel unanimously agrees with CADTHs view that the CDEC was acting in accordance with CADTH's policies in determining whether or not it required additional clinical expertise to complete its review.

3. Stakeholder Input

On the third issue that it is was unclear how the stakeholder input was considered and that, in fact it was misconstrued in the final report, the Panel agrees that the final report was deficient in its explanation of how it reviewed the stakeholder input, but is unanimously satisfied that the CDEC did receive all the stakeholder comments. The Panel strongly encourages the CDEC to be more transparent in its reports about how stakeholder input is considered in the context of the review. This is very important to encourage continued stakeholder engagement and trust in the HTA processes.

4. Deviation from Deliberative Framework

On the fourth issue that the Deliberative Framework is prescriptive on the elements that determine reimbursement recommendations, the panel finds that the list of factors included in the Procedures document is meant to be illustrative and not exhaustive. As a result, the Panel unanimously finds no breach.

5. Deviation from Reconsideration Process

Novartis proposes that given the amount of information provided during the Reconsideration process, the resulting report should have contained significant editorial revisions as evidence that the material was reviewed. The Panel unanimously finds that this is an insufficient reason to find that the CDEC did not review the new data and hence there is no breach. However, again, the Panel strongly recommends that in future CDEC exercise more care in communicating its analyses and outcomes.

6. Scope of the CDEC's Mandate

On the final issue, Novartis argues that in citing safety in its recommendation the CDEC overstepped its mandate, because determining safety is the purview of Health Canada whereas CADTH argued that the CDEC reviews inherently balance safety (side-effects and risks) with efficacy and cost. The Panel unanimously finds no breach.

In closing, as indicated in the opening the Panel finds no breach of procedures, but does recommend that CADTH review its communications for clarity and comprehensiveness. On behalf of the Panel, I would like to thank both the representatives of Novartis and the CADTH Drug Review Team for their presentations, which were clear, concise and thought-provoking, and the helpful answers to our questions. I would also like to thank my fellow panel members, Dr. Anthony Fields and Jonah Dupuis for their candour, insight and active participation in our deliberations, and finally the CADTH corporate services team for their support in arranging our meetings and teleconferences.

Sincerely,

Diane McArthur
Chair, Procedural Review Panel

c Dr. A. L. A. (Tony) Fields
Jonah Dupuis