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

FROM: Diane McArthur
Chair, Procedural Review Panel

Date: March 1, 2023

RE: Procedural Review of pegvaliase (Palynziq ®)

Dear Ms. Bowes,

I am writing on behalf of the Procedural Review Panel (Panel) regarding the results of our recent review of the procedures followed by the CADTH in its review of pegvaliase (Palynziq ®). The purpose of this review is to determine if any errors were made by CADTH with respect to its adherence to the procedures as outlined in the *Procedures for CADTH Reimbursement Reviews* (November 2022 version) and is not related to other content or to the scientific validity of the analyses leading to the conclusions in the final recommendation.

In general, the Panel was impressed by the quality and thoughtfulness of the materials presented by BioMarin Pharmaceutical Canada (BioMarin) and CADTH. That said, the Panel felt that many of the detailed arguments put forward by the applicant were more suited to an appeal of CDEC's recommendations, based on a challenge of their scientific validity, than to whether there was a breach of CADTH's Procedures. The Panel focused its deliberations on the elements that addressed potential breaches of Procedures.

The pegvaliase (Palynziq ®) application did raise new issues related to:
1. the relationship between CADTH's articulated guiding principle of evidence-based recommendation making and the procedures as set out in the Procedures document, and
2. the definition of a substantial change in a recommendation.

BioMarin raised the following issues for the Panel to consider:
1. The Reimbursement Renewal Conditions were not consistent with CDEC's Mandate
2. Adequacy of Clinical Expertise
3. CDEC did not include Stakeholder Input during the Recommendation phase
4. CDEC Deviated from its own Deliberative Framework
5. CADTH failed to follow the Procedures for Reconsideration Options
6. The Reimbursement Renewal Conditions are not supported with CDEC statements

With respect to the first five issues, the Panel was unanimous in its findings that there was no Procedural breach. On issue six, the Panel had considerable debate but ultimately determined by split vote that there was no Procedural breach.

Panel meeting with BioMarin and CADTH

The Panel was convened on February 13, 2023 to hear presentations from BioMarin and the CADTH Drug Review Team with respect to the CADTH/CDEC final recommendation for pegvaliase (Palynziq ®). In preparation for the meeting, the Panel reviewed the following materials:

1. Meeting agenda
2. Procedural Review Application submitted by BioMarin
3. Slide Decks prepared by BioMarin and CADTH
4. Procedures for CADTH Reimbursement Reviews (November 2022 version)

The Panel reconvened on February 22, 2023 to review the following materials requested in follow-up to the February 13, 2023 meeting:

1. CADTH documentation regarding the determination of the renewal conditions included in the CDEC recommendation following reconsideration.

Panel Deliberations:

As set out above, the sponsor raised six issues. There is considerable overlap between the issues as set out by BioMarin, and this report will address the substance generally following the way they were presented, but with some overlap, leaving the issue of the determination of funding criteria to the end.

The Panel debated whether or not the alignment of CADTH's recommendations with available evidence was within our mandate. The Panel concluded that it is not for the Panel to adjudicate *how* the evidence is weighed, but only *whether* the evidence is duly considered. In the case of pegvaliase (Palynziq ®), the Panel was satisfied that the available evidence was canvassed by CADTH and considered by CDEC. The Panel therefore concluded that there was no breach of the Procedures in this regard.

With respect to involvement of clinical expertise, the CADTH documentation demonstrates that two clinical specialists with expertise in the diagnosis and management of pediatric and adult patients with phenylketonuria (PKU) who have inadequate Phe control were consulted, and input from a clinical group made up of three physicians who care for adult patients with PKU in Canada was received as part of the review. This is consistent with the Procedures.

On the issue of Stakeholder input, the documentation indicates that the consultation processes detailed in the Procedures were followed and input was received. We continue to encourage CADTH to articulate more clearly the consideration given to such input in its recommendation documents.

Regarding issue four, BioMarin repeats their concern regarding Stakeholder input as well as that CADTH did not follow evidence in its decisions The CADTH materials demonstrate a broad ranging canvas of evidence that included clinical data, patient needs and preferences as well as clinician expertise on how best a therapy may fit within the Canadian practice landscape. The CADTH materials document the active discussion of the various types of evidence described above, which in part is reflected in the differing views cited by BioMarin to support issue six.

The Panel spent considerable time debating the inclusion of the eligibility and renewal conditions recommendations from the two perspectives raised by the applicant. First, that there should have been an opportunity for input as the conditions represent a "substantial change" and should have triggered a re-issue and opportunity for stakeholder input. And second, BioMarin argues the conditions are not evidence-based.

The Panel has empathy for the concerns and impact on the patient population that the introduction of conditions may have, and the lack of opportunity to comment on them. However, in this instance the Procedures document is quite clear on the two specific criteria for the circumstances under which CADTH will issue a revised draft recommendation; the term "specifically" is used to introduce them. As a result, the Panel finds that the addition of conditions to the recommendation does not meet the definition of "a substantial change," and therefore there is no Procedural breach. As CADTH undertakes a substantive review of the Procedures per our earlier recommendations, we suggest that they consider whether or not the criteria for issuing a revised draft recommendation following reconsideration should be amended.

On the issue of evidence, it is important to note that the role of a Health Technology Assessment (HTA) body is significantly different from that of a regulatory (Health Canada) approval. The Health Canada approval indicates that a drug is sufficiently safe and effective for distribution and sale in Canada, and includes approval of the product monograph that that will be issued by the manufacturer. HTA focuses on whether and how best to introduce a product within a health care delivery system. Safety and efficacy as endorsed by Health Canada and described in the product monograph are necessary but not sufficient for recommendation. Additional considerations include other dimensions of value, including need, perspectives of patients, providers and health systems served, cost-effectiveness, budget impact, and comparison with available therapies. The perspectives from participating health systems include the exigencies of delivering the new product to patients within their jurisdictions. The materials submitted by CADTH indicate that there was consideration of patient needs for, response to, compliance with and tolerance of pegvaliase (Palynziq ®), with input from BioMarin's submission, and also from the clinicians engaged, the patient group and provincial jurisdictions. Ultimately, the Panel was split on whether or not the lack of specific evidence from the clinical trial alone to support CDEC's recommendation for patient eligibility and renewal criteria constituted a breach of the Procedures. By a vote of 2-1, the Panel found that there was no breach.

Once again, I would like to thank my fellow Panel members Jonah Dupuis and Dr. Anthony Fields for the open, respectful, and frank debate on the issues raised in this Review. Their willingness to challenge all aspects of the process and their clinical and professional experiences dealing with both patients and clinicians has been exceedingly helpful in rounding out our discussions. We also express our gratitude to the presenters for their thought-provoking presentations.

Sincerely,

Diane McArthur,
Chair, Procedural Review Panel

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