CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta)

(Vertex Pharmaceuticals (Canada) Incorporated)

Indication: Trikafta (elexacaftor/tezacaftor/ivacaftor and ivacaftor) is indicated for the treatment of cystic fibrosis (CF) in patients aged 2 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

November 9, 2023

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0776-000
Brand name (generic)	Trikafta (elexacaftor/tezacaftor/ivacaftor and ivacaftor)
Indication(s)	Cystic fibrosis, F508del CFTR mutation, two years and older
Organization	Health Advisory Council, Cystic Fibrosis Canada
Contact information	Name: Dr. Mark Chilvers, [redacted]

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

The Health Advisory Council appreciates the draft recommendation and agrees that Canada's public drug programs should fund ELZ-TEZ-IVA for 2-5 year olds. The recommendation is generally thoughtful and appropriate for this age group. A 12-month evaluation of treatment is very appropriate and a welcome recommendation. As highlighted by the clinical experts consulted by CADTH we have concerns about how the BMI renewal requirement will be perceived and its potential impact on access going forward. The main treatment goal in the 2–5-year-old cohort is preventing progression of multi-system disease, particularly minimizing the evolution of structural lung disease that is present at birth. In addition, data suggests there may be pancreatic recovery within this population with early introduction. Within this age group it is difficult to obtain objective outcomes of response as there aren't standardized routine clinical measurements that can support this. Therefore, the recommendation of clinical judgement to assess response would be the most appropriate for this age group.

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	☐

The CDEC showed great consideration of the available evidence and stakeholder perspectives. Where challenges in the evidence base existed, CDEC sought clinical expertise. We agree that CF clinicians are the experts in CF care, which is why we believe that CF clinicians should be empowered to use their discretion and the *Canadian Clinical Consensus Guideline for Initiation, Monitoring and Discontinuation of CFTR Modulator Therapies for Patients with Cystic Fibrosis* (the clinical consensus guideline) to determine who should start, continue and discontinue ELZ-TEZ-IVA.

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

The reasons for the statement for the recommendation are stated clearly. The reference to BMI Z-score as a marker of response is not routinely tracked in pediatric CF clinics. The score is useful in identifying at risk CF patients but as stated in the report BMI may vary over time. An appropriate use of BMI would be children who fall below the BMI-Z-score 3rd centile and alternative causes of weight loss excluded, would be deemed non-responsive. The recommendation emphasizes continuing benefit: Maintaining health is the primary goal of treatment for this age group. As clinicians, the treatment focus for children is slowing the progress of the disease and maintaining overall health.

The *Canadian Clinical Consensus Guideline for Initiation, Monitoring and Discontinuation of CFTR Modulator Therapies for Patients with Cystic Fibrosis* recommends a monitoring schedule for this patient group and overall, the response should be determined by the clinician over the 12-month period.

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

As stated above the suggestion of increased BMI Z score as a renewal condition is not in keeping with the goals of standard clinical practice. Within CF clinical practice it is used as a marker to identify individuals at risk of obesity or malnutrition. As stated in the report this may vary overtime due to growth, activity or illness. The implications from the report are that children who are otherwise relatively healthy could lose access to drug because of these "normal" variations in BMI. CF clinician experts are well positioned to decide on treatment responses for their patients together with the consensus guidance document. A potential BMI response for renewal t is not the whole picture of clinical response and removal of this caveat would be appropriate. .

Specifically, we are calling on CDEC to amend the draft recommendation to read: "For renewal after initial authorization, the physician must provide evidence of continuing benefit from treatment with ELZ-TEZ-IVA for subsequent renewal of reimbursement. Patients on therapy should be monitored for response ~~(e.g., no decrease in BMI z score)~~ using clinical judgment and/or standard procedures". However, if BMI is required to stipulate a BMI-Z-score <3rd centile and all alternative causes of weight loss excluded, would be deemed non-responsive. In addition, the recommendation states that it is reasonable to extrapolate efficacy data from older age groups and that clinician input on the benefit of starting early is important in creating a more robust evidence base. The introduction of ELZ-TEZ-IVA in 2-5 year olds presents an opportunity for CADTH and our public drug programs to access and contribute to long term data that shows the stabilization of FEV1 in older populations. These data were not available for previous CADTH reviews of ELZ-TEZ-IVA but now represent a shift toward treating this drug as a disease modifying medication. Data like these should help to eliminate any criteria other than the patient having a CF diagnosis, meeting the age indication and carrying a responsive mutation.

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

Highlighting BMI may be misinterpreted by reimbursement bodies as a rule that must be followed rather than an example of a potential health indicator. As detailed above, CDEC must clearly state that no decrease in BMI z-score<3rd centile OR no stabilization or improvement in lung health OR opinion of the CF clinician that ELZ-TEX-IVA is resulting in unacceptable side effects or not having a clinical benefit. It is not clear how much of a fluctuation in BMI would be indicative of a meaningful and actionable difference to renewal of ELZ-TEX-IVA in this age group. It is a potentially dangerous and harmful practice to be quick to cut the drug off if there is some fluctuation in BMI.

The CDEC recommendation that for patients who start ELX-TEZ-IVA treatment between the age of 2 to 5 years old, once they turn 6 should be subject to the discontinuation and renewal conditions in the 6 and older recommendation, but the baseline used should be when the patients initially started treatment with ELX-TEZ-IVA even if that was between the age of 2 to 5. This is not achievable as detailed on the report the initial baseline assessments are completely different and so cannot be compared. This recommendation should be removed. Finally, the recommendation limits reimbursement for those who have undergone lung transplant, a treatment option for people with CF with end-stage lung disease. While CFTR modulators would not be expected to directly improve lung graft function, they have potential to alleviate extrapulmonary manifestations of CF such as chronic

rhinosinusitis and gastrointestinal disease. Of note, paranasal sinuses may act as a reservoir for pathogens following transplantation, therefore treatment of chronic rhinosinusitis with CFTR modulators may reduce respiratory infectious complications after lung transplantation. Evidence is emerging that this therapy may help some post-transplant patients. Rather than limit access in the CDEC recommendation, it should be noted that a CF specialist should be involved in the initiation of CFTR modulators and subsequent monitoring of a CF patient who has undergone lung transplant and commenced on a CFTR modulator. The clinical consensus guideline provides direction here.

[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	☒
Cystic Fibrosis Canada acts as secretariate to the Health Advisory Council and provided assistance in drafting this response.		
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: • 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*
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.

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0776
Name of the drug and Indication(s)	Elexacaftor-tezacaftor-ivacaftor and ivacaftor (Trikafta) For the treatment of cystic fibrosis in patients aged 2 and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator gene
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	X
	No requested revisions	☐

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification.
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification.
c) Implementation guidance

Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here.

Further guidance is required regarding how drug plans can implement objective renewal and discontinuation criteria for those 6 years and above who started therapy when they were 5 years or younger. Questions:

- What additional baseline measurements (e.g., FEV1, CFQ-C, CFQ-P) should be required when a patient turns 6 years of age?
- Given that CF is a progressive disease and that patients may have started on therapy before any significant adverse consequences of CF were measurable, what should be required for renewals? For example:
  - Should maintenance of all baseline measurements (including those collected once a patient turns 6) be required?
    OR
  - Is there a specified level of decline in any of the baseline measurements (including those collected once a patient turns 6) that would be acceptable and permit a patient to continue receiving therapy?
    OR
  - Is there a specified level of decline in any of the baseline measurements (including those collected once a patient turns 6) that should result in treatment discontinuation?
    OR
  - Is there some other measure of overall decline not related to baseline measurements that should result in treatment discontinuation?

Note that current criteria for the 6 year and above age group generally require an improvement in one or more of the baseline measurements.

Outstanding Implementation Issues

In the event of a positive draft recommendation, drug programs can request further implementation support from CADTH on topics that cannot be addressed in the reimbursement review (e.g., concerning other drugs, without sufficient evidence to support a recommendation, etc.). Note that outstanding implementation questions can also be posed to the expert committee in Feedback section 4c.

Algorithm and implementation questions
1. Please specify sequencing questions or issues that should be addressed by CADTH (oncology only)
1. 2.
2. Please specify other implementation questions or issues that should be addressed by CADTH
1. 2.

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0776-000
Brand name (generic)	Trikafta (elexacaftor/tezacaftor/ivacaftor and ivacaftor)
Indication(s)	Cystic fibrosis, F508del CFTR mutation, two years and older
Organization	Cystic Fibrosis Canada
Contact information[a]	Dr. Paul Eckford, [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. CF Canada agrees that our public drug programs should fund Trikafta for 2-5 year olds with at least one copy of the F508del mutation, as well as those two years of age an older who have other mutations that may respond to treatment. Overall, we are pleased with the attention paid to the challenges faced in obtaining baseline and renewal measurements in the 2-5 year old population. However, we are concerned about how the BMI measure may impact access going forward. We agree with the renewal reasoning that "Clinical experts have noted that it is difficult to obtain objective measurements to assess response to treatment in patients aged to 2 to 5 years." In light of this acknowledgement, the renewal criteria should primarily be based on overall clinical judgement of CF clinicians, who are the experts. BMI is but one indicator and a minor drop in BMI at one time point is not necessarily an indicator of lack of clinical benefit or lack of protective benefit in maintaining a healthy condition.

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? BMI is generally a good indicator of health in children and young adults with CF. However, like most children, even those with cystic fibrosis can experience fluctuations in weight that may not be due to CF, such as growth spurts, increased exercise as the result of treatment, and the common flu. Eventually, they simply grow up and their BMI stabilizes. We recently heard of a case in which a teenager lost coverage for Trikafta because they had a growth spurt. This is unacceptable. The renewal criteria require clinicians to provide "continuing evidence" to continue treatment, and that "patients on therapy should be monitored for response (e.g., no decrease in BMI z-score) using clinical judgment and/or standard procedures". This is too rigid. We believe that the prescribing regimen of all CFTR modulators should be in alignment with the *Canadian Clinical Consensus Guideline for Initiation, Monitoring and Discontinuation of CFTR Modulator Therapies for Patients with Cystic Fibrosis* (the clinical consensus guideline). By using the consensus guideline, clinicians can determine access based on the medical needs of their individual patients.

There continues to be a lack of access to this therapy for a significant population (approx. 200 individuals, perhaps many more) in Canada with a variety of rare mutations, but lacking the most common mutation. Nearly 200 gating, conductance, trafficking and other mutations have been shown by in vitro laboratory evidence to respond to this triple therapy. The US FDA has expanded

the label for Trikafta in the US based on laboratory evidence to 176 mutations. Canadians are getting sicker while CF patients in other countries have access to this life-saving therapy. Significant RWE from US patients with rare mutations on this therapy, and the world-leading compassionate access program in France for all individuals who can respond, is readily available now in the scientific literature and should be used to provide access to all who can benefit, immediately. This is not new information; we have indicated that there is evidence supporting use of Trikafta in individuals with many rare mutations in past submissions. CADTH can and must make a recommendation to provincial plans to fund this drug for **all who can benefit**, as many of our international counterparts have already done.

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. Generally, the rationale and implementation recommendations are well thought out and show the length CDEC went in wrestling with the available evidence, diagnostic and maintenance tests. Still, the reliance on BMI as a renewal requirement will leave children whose weight may fluctuate for reasons other than malnutrition behind, causing them to lose access to this drug even if they experience overall clinical benefit. This requirement must be removed.

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.
Include comments around QALY, pre-negotiated, null.

We believe that the reimbursement conditions were clearly stated. We continue to take issue with a QALY of $50,000 to measure the impact of drugs for rare diseases, as well as the call for a significant price reduction on the single greatest innovation in the history of cystic fibrosis: Trikafta. That our public drug programs moved so quickly to fund the drug for 6+ is a testament to how joint negotiation through the pCPA can drive prices down while also delivering excellent value in therapy. Despite this, CDEC chose to use the drug's pre-negotiated list price in its re-assessment, thereby overestimating the cost of the drug while also negating the fact that our public payers negotiated a price they are clearly comfortable paying.

The $50,000 QALY that CADTH uses is decades old, out of touch, and puts access to life-saving and life-changing rare disease drugs at risk. A recently published article by Maarten, J. *et al* concludes that "conventional (cost-effectiveness analysis) was developed when the prevalence, heterogeneity, and outsized economic impact of rare diseases were poorly understood and there were no effective treatments. This has produced a pharmacoeconomic valuation context that continues to emphasize a particular extra-welfarist utilitarian approach to societal healthcare resource allocation that favors treatments for more common (and often less devastating) diseases". We whole-heartedly agree. CADTH needs more meaningful and modern methods to assess CEA as it relates to drugs for rare diseases like Trikafta.

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

Appendix 1. Conflict of Interest Declarations for Patient Groups

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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	*Dr. Paul Eckford*
Position	*Chief Scientific Officer*
Date	*6/11/2023*
☒	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	☐
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
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	☐	☐	☐	☐