CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

Elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta)
(Vertex Pharmaceuticals (Canada) Inc.)

Indication: Cystic fibrosis, F508del CFTR mutation, 6 years and older

June 3, 2022

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0710-000
Brand name (generic)	Elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta™)
Indication(s)	For people living with cystic fibrosis aged 6 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene
Organization	Cystic Fibrosis Canada's Accelerating Clinical Trials Network (also called CF CanACT) Executive Committee.
Contact information[a]	Name: Dr. Bradley Quon on behalf of CF CanACT Title: Staff Respirologist, St. Paul's Hospital, Vancouver, BC; Associate Professor of Medicine, University of British Columbia [redacted]

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

The CF CanACT Executive Committee are very pleased that CADTH has recommended elexacaftor/tezacaftor/ivacaftor (ETI) for reimbursement for people living with cystic fibrosis aged six years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. We are also pleased to note that the Canadian Drug Expert Committee recommended reimbursement of ETI for patients with ppFEV1 > 90%. This is important, since 59% of CF patients between 6-17 years of age and 20% of adults have a ppFEV1>90%. However, we have some concerns about some of the conditions for reimbursement included in the draft recommendation:

Page 4, Table 1. Renewal Condition Point 7

We are pleased that the draft recommendation provides a number of options to demonstrate benefit after six months of treatment including no change in BMI and a 4-point increase in the CFQ-R Resp domain. These are reasonable as they are important outcome measures but we encourage CADTH to preserve all options in the final recommendation. We would be concerned with an exclusive focus on the requirement for an improvement in ppFEV1 of at least 5% for renewal of therapy **OR** a decrease in the total number of days for which the patient received treatment with oral and/or IV antibiotics for pulmonary exacerbations compared with the 6-month period prior to initiating treatment.

- The majority of patients with CF aged 6 years of age will have normal lung function. (The median lung function for 6-year old's is ppFEV1 102%). Thus, due to a ceiling effect, it may be difficult for patients with CF in this age group to achieve an increase of 5% in FEV1 following commencement of ETI. A better indicator would be stabilization of lung function over time (i.e., attenuation of usual decline in lung function). This is also indicated in the clinical guidelines developed by CF clinicians.
- In this age group, the number of pulmonary exacerbations, hospitalizations or the use of antibiotics is low, so this measurement may not accurately reflect the true response to ETI.

Table 1. Renewal Condition 8

We are concerned about the recommendation for annual renewal.

- The concern is not regarding the recommended criteria, rather, the burden of time it will take to complete the assessments and paperwork associated with having the drug funded for individual patients on a yearly basis, across public and private payers.
- CF clinicians are already struggling to meet the initiation and reimbursement requirements of Canada's public and private payers. The addition of 6-11-year olds and individuals who are 12 years of age or older with a ppFEV1 >90% will increase this burden. CF clinicians are experts in CF care and have developed a consensus guideline to inform their decision-making on access to therapy that includes a schedule for baseline evaluation and monitoring of patients aged 6 years and older. Unnecessary administrative hurdles to continuation of therapy should be removed.
- We know that the decline in FEV1 with age is greater in persons with CF than in the non-CF general population. Studies have shown that CFTR modulators can decrease this decline over short periods, but we do not yet have evidence as to the long-term effect on FEV1 decline. A person with a moderate response to CFTR modulator with an improvement in ppFEV1 of 6% from baseline, for example, could see this margin eroded over time compared to the original baseline if the decline in FEV1 on ETI is still greater than the decline in the non-CF population, from which the ppFEV1 are calculated. That person with CF would still have a positive therapeutic effect from the medication by slowing the ppFEV1 decline and showing improvement in other measures of health.

Page 5, Table 1. Discontinuation, point 9.

- CADTH has rightly pointed out that solid organ transplant patients were excluded from any of the randomised clinical trials. While it would have been difficult to include a person with CF who has had a lung transplant in a clinical trial where the primary outcome is FEV1, this does not mean that they would not respond to ETI. Apart from the lungs, other organs (sinuses, pancreatic disease, and intestinal disease) are affected in patients with CF and ETI may improve these extrapulmonary manifestations of CF.
- From published, retrospective and several observational trials involving patients with CF who have had a lung transplant, it appears, that ETI has a role to play in post-lung transplant CF patients in improving their extrapulmonary manifestations such as, improving BMI, sinus and GI symptoms and decreasing hemoglobin A1c in patients with diabetes.
- We urge CADTH to reconsider their broad discontinuation statement for solid organ transplants.

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	☒

Page 5, Table 1. Discontinuation, point 9.
"Patients who had had a solid organ transplantation were excluded from the main studies of ETI and Canadian clinical experts indicated that the treatment should be discontinued in patients who have received lung transplantation".

- The above is a broad statement with no discussion points on page 6 to support this recommendation.
- The committee failed to include any observational or retrospective trials in this group of patients, while for patients with an FEV1<40%, the committee included observational studies in their discussion.

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

Page 4, Table 1. Initiation Reimbursement Condition 3: Implementation

While it is important to do all the baseline assessments indicated, not all of the assessments are part of routine care. We are concerned about the extra time required by health care professionals to administer these additional assessments. As a result, we recommend that clinics be provided with additional resources to perform these additional assessments.

- The Cystic Fibrosis Questionnaire-Revised (CFQ-R) needs to be administered to a child by a healthcare professional. On average this takes about 20 minutes. In addition, a parent is also administered the CFQ-R parent edition. To do both will take approximately 30 minutes. Most CF clinics do not administer the CFQ-R on a regular basis due to time constraints.
- To interview the patient, and establish the number of days on antibiotics, days of hospitalization, or number of respiratory exacerbations requires a retrospective chart audit. This again would require extra time from a healthcare professional.

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 th s person f comments requ re c ar f cat on.

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: Dr. Bradley Quon • Clinician 2: N/A • *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.
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	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0710
Name of the drug and Indication(s)	Elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta) for treatment of cystic fibrosis in patients aged 6 years 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. "6 years and older" - recommendation is broadening criteria without (In BC's view) sufficient evidence to do so.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Request the addition of more context on the level of evidence used to inform the recommendation.
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.

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0710-000
Brand name (generic)	Trikafta (elexacaftor/tezacaftor/ivacaftor and ivacaftor)
Indication(s)	Cystic fibrosis, F508del CFTR mutation, 6 years and older
Organization	Cystic Fibrosis Canada
Contact information[a]	Name: Dr. John Wallenburg, Chief Scientific Officer

Stakeholder agreement with the draft recommendation

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

Cystic Fibrosis Canada (CF Canada) agrees that Canada's public drug programs should reimburse Trikafta (ETI) for this cohort. We are pleased that the draft recommendation for those 6+ comes without any upper lung function start criterion.

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	☐

We appreciate CDEC's thoughtful consideration of the evidence and stakeholder submissions. Our clinicians and our patient community are thankful that CADTH has recognized the importance of considering the many benefits and outcomes that patients may experience when taking ETI. We are pleased that CDEC has acknowledged the complexity of CF care and the initiation of ETI. We agree that this makes CF specialists uniquely positioned to prescribe and monitor treatment response. It follows that prescribing and monitoring of ETI should be limited to CF specialists.

CF Canada believes 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), which was developed by CF clinicians specifically for Canadians living with the disease. The guideline is being updated to reflect the new 6–11-year-old Health Canada indication and the growing body of real world evidence (RWE) that demonstrates the impact of ETI on those currently indicated, as well as those who live with rarer mutations and who are post-transplant. There is also emerging evidence on use of ETI in pregnancy to treat mothers and/or fetuses with CF. CF Canada will provide CDEC with the revised guideline when available.

Clarity of the draft recommendation

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

We appreciate that CDEC considered the RWE provided, which is important in paving the way for better access to high value drugs for rare diseases, including precision medicines. In reviewing the RWE, CDEC noted small sample size and lack of comparator group as limitations. For rare conditions, sample sizes will be small and there may be a lack a comparator group. We caution CADTH not to unfairly limit the value of RWE by applying unrealistic demands. These issues will become evident as CDEC considers future applications that may be made for patients aged 2 to 5 years, 18 months to 2 years, and 4 months to 18 months or when evaluating access for individuals who have undergone transplants and those with very rare mutations that can be treated with ETI.

	Yes	☐

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

Reduce the burden on clinics. Many CF clinics are already struggling to meet the initiation and reimbursement requirements of Canada's public and private payers. The addition of 6-11 year olds and individuals who are 12 years of age or older with lung functions of 90% or greater will increase this burden. CF clinicians are the experts in CF care. They use the clinical consensus guideline to inform their decision-making on access to therapy that includes a schedule for baseline evaluation and monitoring of patients aged 6 years of age and older.

Address the unintended use of CADTH recommendations. CADTH's reimbursement reviews are conducted for and with Canada's public drug programs in mind. However, increasingly private insurers are using CADTH recommendations to deny access to life-changing therapies for drugs for rare diseases. This became explicitly clear as clinically eligible patients were turned away for private coverage of ETI based on CDEC's recommended 90% price reduction for implementation of 12+ (which is also reflected in CDEC's 6+ recommendation). This is a significant barrier to access and needs addressing.

CF Canada would like to acknowledge Canada's public drug programs efforts to cover ETI quickly. Nevertheless, there are still people who are falling through the cracks in jurisdictions that charge high deductibles for public access or have convoluted coordination between public and private payers. This is an implementation issue that must be addressed to ensure needed access. CADTH can help by reinforcing that its recommendations serve and are designed for Canada's public drug programs.

Cystic Fibrosis Canada recommends that the following issues be addressed in CDEC's implementation guidance:

- Reduce the burden on clinics by reducing requirements where possible and streamlining processes and paperwork required to initiate, monitor and renew therapies. Where needed, jurisdictions should provide additional resources to CF clinics specifically to help them prioritize and thoroughly process patients in a timely manner.
- Address the unintended use of CADTH recommendations to limit access to treatment among private payers. In its recommendations, CADTH should explicitly state that its drug reviews are designed for the public payer market and are not intended to be used in whole or in part to deny access to patients who rely on private coverage.

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

Overall, CDEC's recommended initiation criteria align with the clinical consensus guideline. The guideline calls for treatment of CFTR modulators to be started at the youngest age approved by Health Canada with the goal of attenuating disease progression and improving clinical status.

One area for improvement relates to limiting access to patients with at least one copy of F508del. There is good laboratory evidence to support the use of ETI on other, very rare mutations.

Unfortunately, Canada is behind its international comparators when it comes to regulatory review and reimbursement of drugs for rare diseases. One driver of these access challenges is that Canada rejects certain forms of evidence especially useful for rare disease populations. Canada is without a framework to fairly consider laboratory based predictive tools for precision medicines. Yet, good in-vitro predictive tools exist in Canada (e.g. the Program for Individualized Cystic Fibrosis Therapy (CFIT) at SickKids) in Europe (HIT-CF Europe) and elsewhere that predict individual and mutation class responses of rare mutations to ETI.

In addition, clinicians can both empirically see and explicitly measure the response that such individuals have to a medication. Our regulatory, review and reimbursement bodies do not generally accept such evidence. Both the FDA in the United States and the NHS in the United Kingdom have

accepted in-vitro data to expand access (off-label in the UK) to ETI to an additional 177 mutations (or more). Cystic Fibrosis Canada recommends that CADTH follow the examples of the FDA and the NHS to recommend access for patients with rare mutations through use of laboratory based predictive tools.

CDEC is right to point out that patients who have had a solid organ transplant were excluded from the main studies of Trikafta. The clinical experts consulted by CDEC noted that treatment should be discontinued in patients who have received lung transplant given that lung transplants are a last resource for people with CF with end-stage lung disease. However, although CFTR modulators are not expected to improve the function of grafted lungs, they do have potential to alleviate extrapulmonary manifestations of CF such as chronic rhinosinusitis and gastrointestinal disease. Paranasal sinuses may act as a reservoir for pathogens following transplantation, so treatment of chronic rhinosinusitis with CFTR modulators may reduce respiratory infectious complications after lung transplantation. We propose that CADTH reconsider its blanket exclusion of patients post-transplant and recommend that a CF specialist have the ability to initiate and monitor ETI therapy in a post-transplant CF patient when there is a demonstrated medical need.

[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	Dr. John Wallenburg
Position	Chief Scientific Officer
Date	03-06-2022
☒	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	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0710
Brand name (generic)	PrTRIKAFTA® (elexacaftor/tezacaftor/ivacaftor and ivacaftor)
Indication(s)	Treatment of cystic fibrosis in patients aged 6 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator gene.
Organization	Vertex Pharmaceuticals (Canada) Inc.
Contact information[a]	[redacted]

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

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	☒

Regarding the following statement on Pg. 3 of 9 in the CADTH recommendation regarding the Pharmacoeconomic Report that reads *"However, the sponsor also assumed that treatment with a CFTR modulator would slow the long-term rate of decline of ppFEV$_1$ when compared with the rate of decline of patients not receiving disease modifying treatment. In the absence of available data with ELX/TEZ/IVA in support of this assumption..."* - Vertex would like to respectfully highlight that at the time of submission, results from the interim analysis of the open-label extension study of TRIKAFTA were already published and demonstrated maintenance of ppFEV$_1$ over 96 weeks of additional treatment (Daines CL, et al. Poster presented at the NACFC Annual Meeting, November 2021). Additionally, since the submission, the registry matched analysis comparing the long-term rate of ppFEV$_1$ decline between patients treated with TRIKAFTA and untreated registry controls has been completed and the results will be presented via oral presentation at European Cystic Fibrosis Society Annual Meeting on June 10^h, 2022. Based on the available evidence to date, Vertex respectfully disagrees with CADTH's assessment that there is no evidence to support modeling TRIKAFTA treatment-related reduction in the long-term lung function decline; assuming zero treatment effect is not supported by the evidence or clinically plausible.

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

Lung transplantation remains an option for CF patients with severe lung disease. Since ELX/TEZ/IVA (ETI) was launched, there have been several retrospective and observational studies examining its use in post-transplant patients. A recent study from the CF Lung Transplant Consortium (CFTLC) on nearly 100 patients demonstrated that for the majority of these people with CF, ETI was well tolerated and adjustments to immunosuppression were clinically feasible. Initiation of ETI after lung transplant was significantly associated with improved hemoglobin A1c, increased hemoglobin levels for those with anemia and decreased frequency of antibiotic prescriptions (1), suggesting that ETI has clinical benefit through extra-pulmonary effects (1). ETI also seems to be associated with

improved pulmonary and extra pulmonary quality of life and manifestations of diseases in some published case studies (2,3).

As ETI is not contraindicated in patients who have underwent lung transplant surgery, as per the Health Canada approved Product Monograph (4) and given the evolving evidence of ETI use in these patients, Vertex respectfully requests that these patients are not excluded from being eligible for ETI.

1. https://doi.org/10.1016/j.jcf.2022.04.009
2.https://www.cysticfibrosisjournal.com/action/showPdf?pii=S1569-1993%2821%2901611-8
3. https://www.jhltonline.org/article/S1053-2498(21)02482-7/fulltext#:~:text=DOI%3Ahttps%3A//doi.org/10.1016/j.healun.2021.08.009
4. https://pi.vrtx.com/files/Canadapm_trikafta_en.pdf

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

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

Regarding the first initiation criteria, **baseline spirometry measurements of FEV_1 in litres and percent predicted (within the last 30 days),** Vertex respectfully requests that CADTH consider aligning to the criteria of **within 3-months**, which the majority of jurisdictions (AB, ON, NFLD, NS, MB, YK, and NB) require today for those ages 12+ in order to limit disruption and confusion to clinicians/patients and ensures equitable, timely access.

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