Canada's Drug Agency
L'Agence des médicaments du Canada

CDA-AMC REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta)

(Vertex Pharmaceuticals (Canada) Incorporated)

Indication: Trikafta (elexacaftor/tezacaftor/ivacaftor and ivacaftor) 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 or a mutation in the CFTR gene that is responsive based on in vitro and/or clinical data.

October 4, 2024

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	**SR0837-000**
Brand name (generic)	elexacaftor/tezacaftor/ivacaftor and ivacaftor (ETI)
Indication(s)	Cystic fibrosis, F508del or responsive CFTR mutation, 2 years and older
Organization	Cystic Fibrosis Canada
Contact information[a]	Name: Kim Steele, Director, Government and Community Relations, [redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
Yes, but greater clarity is needed in the final recommendation regarding mutations that may respond but are not yet captured in the evidence base. The recommendation requires the conditions of Table 1 to be met, but the implementation guidance is unclear. More information is provided in clarity section below.		
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	☐
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒

Rationale is clear for the 152 mutations shown to clinically response, and for the 79 shown to respond through in vitro evidence submitted by the manufacturer, but not for mutations that may respond but are not yet captured in the evidence base. This lack of clarity may lead to confusion regarding public coverage of the drug for those who have mutations that may respond to ETI.

It is unclear how jurisdictions might implement access for those with mutations that may respond but are not yet in the evidence base. On page 12 of the draft recommendation CDEC rightly quoted CF CanACT's submission "for those with rare CFTR mutations, where data to support the use of ELXTEZ-IVA is very limited, it is **incumbent on regulators to use all available**

evidence or generate the evidence needed to allow access to this life-saving drug as each patient's life may depend on access to this medication". This must be part of the recommendation itself, not just background.

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

More detail is required. For example, in Table 1, section 1 "implementation guidance" states "this includes the 152 non-F508del mutations in the CFTR gene…". It should state "this includes – but is not limited to – the 152 non-F508del mutations in the CFTR gene…". Without this clarification some public drug programs may choose to exclusively fund the 152 mutations in the product monograph, which will leave people with rare mutations that may respond to ETI but are not yet captured in the evidence base behind.

[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. Paul Eckford*
Position	*Chief Scientific Officer*
Date	*September 25*
☒	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	**SR0837-000**
Brand name (generic)	elexacaftor/tezacaftor/ivacaftor and ivacaftor (ETI)
Indication(s)	Cystic fibrosis, F508del or responsive CFTR mutation, 2 years and older
Organization	Cystic Fibrosis Canada's Accelerating Clinical Trials Network (CF CanACT)
Contact information	Name: Dr. Jonathan Rayment

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
People with CF who have rare mutations (i.e. do not have a copy of the F508del CFTR mutation) have the greatest unmet need. While Health Canada has approved use of ETI in those who have mutations that are responsive based on clinical and/or in vitro data, without reimbursement through public drug programs and private insurance this therapy is out of reach. While we agree with the recommendation, we have concerns about the implementation guidance in Table 1, as detailed below.		
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	☐
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒
According to the Canadian Cystic Fibrosis Registry, 236 people with CF have rare mutations known to respond to ETI (142 mutations in the product monograph) along with 61 who have one of 10 Kalydeco-responsive mutations also now indicated for Trikafta. A further 177 individuals in Canada carry mutations that may respond, but for whom evidence is not yet available. The implementation guidance in Table 1 does not include how to approach the latter group, though the recommendation seems to suggest that evolving evidence should be considered in the reimbursement decision. Greater clarity is required to ensure that evolving evidence of ETI-responsiveness can be efficiently incorporated into reimbursement decisions.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
It is the opinion of this body that medically and ethically, any patient who carries at least one CFTR mutation where there is evidence of ETI-responsiveness should have access to this disease modifying therapy. This recommendation should acknowledge that evidence is constantly evolving.		

The recommendation is for patients aged 2 years and older who have at least one mutation in the CFTR gene that is responsive based on clinical and/or in vitro data. We suggest that the implementation guidance in Table 1 must be amended to reflect the broad nature of the Health Canada indication and CDEC's recommendation. The guidance should not focus exclusively on the 152 non-F508del mutations listed in Table 12 of the Health Canada product monograph, rather it should clarify the concept of ETI-responsiveness to allow for the incorporation of rapidly evolving evidence in reimbursement decisions.

The draft recommendation itself referenced CF CanACT's submission where we stated: "for those with rare CFTR mutations, where data to support the use of ELXTEZ-IVA is very limited, it is incumbent on regulators to use all available evidence or generate the evidence needed to allow access to this life-saving drug as each patient's life may depend on access to this medication." We appreciate this reference and the Committee's thoughtful deliberations on the evidence required to support reimbursement in this population. We continue to support this statement and encourage CDEC to recommend broad access based on clear criteria for evidence supporting benefit, including evolving clinical and in vitro evidence. We advocate CDEC to clearly state that clinical and in vitro **evidence can and will likely evolve to include mutations not listed in those 152 from Table 12** of the Health Canada monograph. Further, we advocate for **specific guidance to define the evidence standards and allow the drug programs to implement this evolving evidence** directly without a need to undergo lengthy review process at a federal level.

[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 provided support in preparing this submission.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☐
	Yes	☒
The Canadian Cystic Fibrosis Registry, which is managed by Cystic Fibrosis Canada.		
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: • Dr. Jonathan Rayment		

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	**SR0837-000**
Brand name (generic)	elexacaftor/tezacaftor/ivacaftor and ivacaftor (ETI)
Indication(s)	Cystic fibrosis, F508del or responsive CFTR mutation, 2 years and older
Organization	CF Canada Health Advisory Council
Contact information[a]	Name: Dr Mark Chilvers, Chair, CF Canada Health Advisory Council

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
The Canadian Clinical Consensus Guideline for Initiation, Monitoring and Discontinuation of CFTR Modulator Therapies for Patients with Cystic Fibrosis clearly defines patients who should be treated with a CFTR modulator and recommend this therapy for all patients with CF who have at least one ETI responsive CFTR variant. The recommendation follows the Health Canada indication for those 2 years of age or older who have at least one variant in the CFTR gene that is modulator responsive based on clinical and/or in vitro data provided the conditions listed in Table 1 are met. The HAC has concerns with Table 1, predefining these CFTR variants listed in Table 2, when the product monograph details "a mutation in the CFTR gene that is responsive based on clinical **and/or** in vitro data". Table 2 does not align with this.		
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 would like to thank the committee for the consideration of all input and publishing an updated recommendation which will allow greater access to CFTR modulators and reduce the treatment gap for Canadians with Cystic Fibrosis		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒
In the current recommendation there is treatment inequity as ETI could be used in every patient who meets the Health Canada approved indication. The implementation guidance does not reflect this. Rather, it focuses on 152 non-F508del variants identified in the product monograph. This does not recognise 177(approx. 4% of CF population) Canadians with CF who have rare mutations that may respond to ETI for which there is currently no published evidence. These individuals fall into a "treatment gap" which is unethical and guidance must align with Health Canada approval and product monograph.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒

Rather than specify the 152 non-F508del mutations, the implementation guidance should align with the consensus guideline referenced above and the product monograph. All patients with CF who have at least on ETI responsive CFTR variant should be able to access ETI.

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

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
Cystic Fibrosis Canada provided support in preparing this submission.		

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.

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.

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0837
Name of the drug and Indication(s)	elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta) Indication: Treatment of cystic fibrosis in patients aged 2 years and older who have at least one F508del mutation in the CFTR gene or a mutation in the CFTR gene that is responsive based on clinical and/or in vitro data
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.

List of CFTR mutations (Table 2) to be linked or included upfront to provide clarity of included mutations in relation to the CDEC recommendation.

b) Reimbursement conditions and related reasons

Please provide details regarding the information that requires clarification.

List of mutations in the CFTR gene (Table 2) that are included to be stated in initiation condition (1) column, rather than implementation guidance. For renewal condition (6), consider whether

baseline lung function measurements required prior to beginning treatment with ELX-TEZ-IVA should be considered as an initiation condition instead.
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.

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.
Support strategy
3. Do you have any preferences or suggestions on how CADTH should address these issues?
May include implementation advice panel, evidence review, provisional algorithm (oncology), etc.