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

CDA-AMC REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

fruquintinib (Fruzaqla)

(Takeda Canada Inc.)

Indication: For the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with or are not considered candidates for available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF agent, an anti-EGFR agent (if RAS wild-type), and either trifluridine-tipiracil or regorafenib.

November 15, 2024

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0352-000
Brand name (generic)	Fruzaqla (fruquintinib)
Indication(s)	For the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with or are not considered candidates for available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF agent, an anti-EGFR agent (if RAS wild-type), and either trifluridine-tipiracil or regorafenib.
Organization	Colorectal Cancer Canada
Contact information[a]	Name: Iris Karry

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. The draft recommendation aligns with the patient input that we submitted for this drug and indication.		

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	☐
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.		
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 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	*Iris Karry*
Position	*Patient Education & Research Manager*
Date	*06-11-2024*
☒	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	**PC0352-000**
Brand name (generic)	Fruquintinib
Indication(s)	For the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with or are not considered candidates for available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF agent, an anti-EGFR agent (if RAS wild-type), and either trifluridine-tipiracil or regorafenib
Organization	Colorectal Cancer Resource & Action Network (**CCRAN**)
Contact information[a]	Filomena Servidio-Italiano, [redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
As nicely stated within the recommendation, the therapy is able to address a number of unmet needs for patients undergoing the metastatic journey: "*pERC concluded that Fruquintinib met some of the needs identified by patients as it offers ease of oral administration, provides improvements in OS and PFS, and has manageable side effects*. " Thus, CCRAN is grateful to be in receipt of this funding recommendation.		

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	☐
Yes! Thank you!		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
Yes, the hope is to include a quick provisional funding algorithm update from CDA followed by a pCPA update.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
Yes, thank you. Once again, the hope is to advocate for Fruquintinib's rightful placement in the treatment algorithm, fourth line or earlier.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
Yes, thank you.		

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

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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	*Filomena Servidio-Italiano*
Position	*President & CEO*
Date	*15/11/2024*
☒	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**
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0352-000
Brand name (generic)	Fruzaqla (fruquintinib)
Indication(s)	For the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with or are not considered candidates for available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy.
Organization	CGOEN – Canadian Gastrointestinal Oncology Evidence Network, and other CRC-treating physicians
Contact information[a]	Name: Dr. Howard Lim [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.		

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	☐
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. CGOEN acknowledges that the phrase "*not considered candidates*" was inserted (Table 1: Reimbursement Conditions and Reasons Section 1.2) in terms of the various therapeutic options. This should allow for the needed flexibility in certainty circumstances. There have been many therapy changes over the past few years, and there may be patients who have not been able to receive certain treatments, or who were not considered candidates due to previous funding restrictions.		

Re: 1.2.4 – CGOEN also acknowledges the important implementation guidance regarding patients who did not receive regorafenib since it is not funded, and patients who may have missed an opportunity for *trifluridine-tipiracil* and *bevacizumab.*

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.

Globally there has been a great demand for fruquitinib which has exceeded expectations.

CGOEN recognizes that both Health Canada and CDA diligently worked to see timely market authorization and health technology assessment for fruquitinib. CGOEN is requesting that the pCPA also prioritize negotiations for this treatment to ensure timely access for patients.

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

Appendix 1. Conflict of Interest Declarations for Patient Groups

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Appendix 2. Conflict of Interest Declarations for Clinician 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.
- 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	☐
If yes, please detail the help and who provided it.		
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)*		

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0352-000
Brand name (generic)	Fruzaqla (Fruquintinib)
Indication(s)	For the treatment of adult patients with mCRC who have been previously treated with or are not considered candidates for available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF agent, an anti-EGFR agent (if RAS wild-type), and either trifluridine-tipiracil or regorafenib
Organization	Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee
Contact information[a]	Name: Dr. Erin Kennedy

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.		

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? Note: Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee did not provide input to CDA on this review.		

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.		
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 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.
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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.
- 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	☒
If yes, please detail the help and who provided it. OH-CCO provided secretariat support to the group.		
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	*Dr. Erin Kennedy*
Position	*Lead, Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee*
Date	*15-11-2024*
☒	**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	*Consolacion Molto Valiente*
Position	*Member, Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee* *Medical Oncologist, R.S. McLaughlin Durham Regional Cancer Centre, Oshawa, Ontario, Canada* *Assistant Professor, Department of Oncology, Queen's University, Kingston, Ontario, Canada*
Date	*07-11-2024*
☒	**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	*Dr. Michael Jonathon Raphael*
Position	*Member, Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee*
Date	*07-11-2024*
☒	**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 Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0352
Name of the drug and Indication(s)	Fruquintinib (Fruzaqla) for the treatment of adult patients with mCRC who have been previously treated with or are not considered candidates for available standard therapies.
Organization Providing Feedback	PAG

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.

In table 1, under Prescribing, PAG is concerned about the restriction stating fruquintinib treatment should not be used in combination with other anticancer drugs. Some patients who enroll in clinical trials may require fruquintinib along with other drugs. PAG is asking whether this statement can be less restrictive.

In table 1, under Initiation, PAG requests consistent wording for the reimbursement condition related to patients with untreated CNS metastases as in other reviews (e.g., pERC recommendation for Lonsurf + bev)
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. In table 2, under Generalizability, PAG would like confirmation whether pERC agreed with the clinical experts regarding the use of fruquintinib in patients with small bowel or appendiceal adenocarcinoma.

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. An update to the rapid algorithm is needed. 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.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0352-000
Brand name (generic)	Fruzaqla (fruquintinib)
Indication(s)	For the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with or are not considered candidates for available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF agent, an anti-EGFR agent (if RAS wild-type), and either trifluridine-tipiracil or regorafenib.
Organization	Takeda Canada Inc.
Contact information[a]	[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.

Takeda agrees with pERC's draft recommendation to reimburse FRUZAQLA (fruquintinib) for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with or are not considered candidates for available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF agent, an anti-EGFR agent (if RAS wild-type), and either trifluridine-tipiracil or regorafenib, based on statistically significant and clinically meaningful improvements in overall survival (OS) and progression-free survival (PFS) demonstrated in the FRESCO-2 trial.

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	☐

If not, please provide details regarding the information that requires clarification.

Takeda acknowledges the CDA's re-analysis of the CEM base-case using FRESCO-2 instead of FRESCO to reflect the revised indication population after the original submission, as highlighted in the Economic Evidence section (Table 2, Key Limitations). This context was not mentioned in the Rationale for the Recommendation, where CDA mentions: "Using the sponsor submitted price for fruquintinib and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for fruquintinib was $325,989 per quality-adjusted life-year (QALY) compared with BSC."

Takeda requests CDA to consider the inclusion of the bolded text for greater clarity:
"Using the sponsor submitted price for fruquintinib and publicly listed prices for all other drug costs, the **CDA base-case re-analysis of the** incremental cost-effectiveness ratio (ICER) for fruquintinib **in the 4L setting** was $325,989 per quality-adjusted life-year (QALY) compared with BSC. **The sponsor did not submit a base-case ICER for fruquintinib vs. BSC in the 4L setting due to the sponsor's cost-effectiveness analysis being submitted prior to the revised population indication."**

Similarly, due to the revised indication population since the original submission, the budget impact analysis submitted in the original submission was for 3L+, with subsequent treatment costs included. In the Discussion Points (p.6), "pERC noted that the sponsor's budget impact analysis was not designed to assess the reimbursement of fruquintinib as a fourth-line therapy". Takeda kindly suggests including at the end of that sentence: "… **due to t**he sponsor's budget impact analysis being submitted prior to the revised population indication."

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.

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.

Takeda acknowledges that the reimbursement conditions in Table 1 are clearly stated with the exception in the Feasibility of adoption where it mentions: "given the difference between the sponsor's estimate and CADTH's estimate(s)". In the Budget Impact section, it states the key limitation, and that "the sponsor's base case was maintained".

For clarity, Takeda suggests considering removing the words "given the difference between the sponsor's estimate and CADTH's estimate(s)" since the CDA estimate was not presented.

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