CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

andexanet alfa (Ondexxya)

(**AstraZeneca Canada Inc.**)

Indication: Ondexxya (andexanet alfa) is indicated for adult patients treated with FXa inhibitors (rivaroxaban or apixaban) when rapid reversal of anticoagulation is needed due to lifethreatening or uncontrolled bleeding.

August 31, 2023

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	ST0772
Brand name (generic)	Ondexxya (Andexanet alfa)
Indication(s)	Ondexxya (andexanet alfa) is indicated for adult patients treated with FXa inhibitors (rivaroxaban or apixaban) when rapid reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.
Organization	Canadian Stroke Consortium
Contact information[a]	Name: Dylan Blacquiere ([redacted])

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒
We feel the recommendations should be delayed after ANNEXA-I trial results are available in October 2023 to allow for a much more robust review of current literature.		

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 feel it would be very inappropriate for the committee to submit recommendations as is, without reviewing the only randomized trial completed for a comparison of Andexanet versus PCC.		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☐
No further comment		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☐
No further comment		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐
No further comment		

[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	☐
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: • Dylan Blacquiere • Laura Gioia • Dariush Dowlatshahi		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Andrew Demchuk*
Position	*Chair, Board of Directors, Canadian Stroke Consortium*
Date	*30-08-2023*
☒	**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**
Astra Zeneca	☐	☒	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Ashkan Shoamanesh*
Position	*Neurologist, Hamilton health Sciences; Steering Committee Member, ANNEXA-Ia Trial*
Date	*31-08-2023*
☒	**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.

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	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AstraZeneca	☐	☒	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Eric Smith*
Position	*Professor, University of Calgary; Imaging Database Lead, ANNEXA-I Trial*
Date	*31-08-2023*
☒	**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.

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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Andrew Micieli*
Position	*Neurologist, Trillium Health Partners, Ontario*
Date	*31-08-2023*
☒	**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.

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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.

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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Canadian Stroke Consortium
101-2275 Upper Middle Rd E, Oakville, ON L6H 0C3
Phone: (416) 386-0844 Toll-free: 1-866-386-0844
strokeconsortium.ca

August 30, 2023

Canada's Drug and Health Technology Agency
865 Carling Ave., Suite 600
Ottawa, ON Canada
K1S 5S8 https://goo.gl/maps/5dDXf

Dear CADTH,

Re: Pending CADTH Canadian Plasma Protein Product Expert Committee (CPEC) reimbursement recommendation for Andexanet Alfa (Ondexxya) indication: For adult patients treated with FXa inhibitors (rivaroxaban or apixaban) when rapid reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding

As a group of stroke specialists and on behalf of the Canadian Stroke Consortium (Canada's professional organization for stroke physicians) we would like to provide feedback as a group on the reimbursement recommendation draft. You may not be aware that the randomized trial of Andexanet-alfa versus usual care in intracranial hemorrhage has now been stopped early for efficacy based on interim analysis at half way point of planned enrollment. We all await details of the study results. See press release link: https://www.astrazeneca.com/media-centre/press-releases/2023/andexxa-phase-iv-trial-stopped-early-after-achieving-pre-specified-criteria-on-haemostatic-efficacy-versus-usual-care.html.

Given this very important development we would ask CADTH to hold back recommendations until this data is available to you in October once presented to the international stroke community for the first time at the World Stroke Congress (Oct 10-12, 2023) in Toronto. ANNEXA-I is a randomized trial led by Canadians at the Population Health Research Institute at University of McMaster (https://www.phri.ca/research/annexa-i/). There will be substantial new clinical data available that will allow more robust CADTH review based on proper unbiased comparison of Andexanet-alfa to usual care (which includes PCC use in a substantial proportion of patients) in a global large randomized trial. PCC use was encouraged for those subjects enrolled in the usual care arm. This data is particularly crucial for a comprehensive evaluation, since you have determined PCC to be the standard of care for FXa inhibitor reversal based on the draft recommendations provided. It would be very important for you to see how PCC stands up to Andexanet-alfa with robust randomized data that was not included in this CADTH submission. There have been no prior randomized trials done for such a comparison of Andexanet versus PCC.

We cannot speak to cost benefit of Ondexxya as we are not privy to PCC and Andexanet costs to Canadian Blood Services. Hopefully once the full analysis of ANNEXA-I is available and these costs known, a robust cost effectiveness analysis can be completed. We had attempted such in the past but this had significant limitations given the potential biases introduced with non-randomized data comparing Andexanet with PCC and the use of previous costing information that was United

Canadian Stroke Consortium
101-2275 Upper Middle Rd E, Oakville, ON L6H 0C3
Phone: (416) 386-0844 Toll-free: 1-866-386-0844
strokeconsortium.ca

States based. See reference: *Micieli A, Demchuk AM, Wijeysundera HC. Economic Evaluation of Andexanet Versus Prothrombin Complex Concentrate for Reversal of Factor Xa-Associated Intracranial Hemorrhage Stroke 2021 Apr;52(4):1390-1397.*

If these recommendations are finalized now before ANNEXA-I trial data is reviewed it could result in substantial delay to access for Canadians as it would result in a CADTH resubmission process that can take many additional months. Canadians with intracranial hemorrhage would miss out on receiving a therapy such as Andexanet-alfa with the delays incurred by resubmission to CADTH. A robust treatment effect is likely given ANNEXA-I stopped early for efficacy. Such delay could be a most unfortunate scenario especially given the severity of outcomes FXa inhibitor related intracranial hemorrhage patients suffer.

Sincerely,

Dylan PV Blacquiere, MD, MSc, FRCPC
Chair, Policy and Advocacy Committee, Canadian Stroke Consortium
Assistant Professor of Medicine (Neurology), University of Ottawa
The Ottawa Hospital, Civic Campus

Andrew M. Demchuk, MD, FRCPC
Chair, Board of Directors, Canadian Stroke Consortium
Director, Calgary Stroke Program
Professor, Departments of Clinical Neurosciences and Radiology
Deputy Dept Head, Department of Clinical Neurosciences
University of Calgary

On behalf of the Canadian Stroke Consortium

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	ST0772
Brand name (generic)	Ondexxya (Andexanet alfa)
Indication(s)	Ondexxya (andexanet alfa) is indicated for adult patients treated with FXa inhibitors (rivaroxaban or apixaban) when rapid reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.
Organization	ER Journal Club, GTA
Contact information[a]	Name: Dr. Indy Ghosh

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.

While we respect the immense work that the committee has put into this review, we urge you to consider the Real World evidence, the ICH trial as well as the community of ER physicians across Canada and what they would tell you. Both CAEP and Thrombosis Canada openly hosted teaching platforms on the value of idarucizumab as a specific reversal agent for Dabigatran as a tool to aid clinicians in massive hemorrhage cases when the patient is on Dabigatran. In fact, the bleeding protocols presented at CAEP had a separate pathway than using PCC or aPCC in Dabigatran bleeding cases because of the availability of a specific reversal agent.

There was a huge volume of feedback on the availability and access to specific reversal agent for the direct Factor Xa inhibitors; indeed, many clinicians noted that the bigger need was to have access to the specific reversal agent for Rivaroxaban, Apixaban and/or Edoxaban as the prevalence of these drugs in our community was much larger.

We respectfully request the committee to please re-examine their recommendation in light of this information.

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?

The evidence for current standard of care to use PCC or aPCC in FXa inhibitor major bleeds is very poor. Compared to this evidence, the current and emerging evidence both in terms of clinical trials as well as real world data, the case for Andexanet is inherently stronger. Family members and the public are becoming more and more well educated in options for treatment and there have been cases where we have been asked why this is not available in Canada yet when it is in use in both USA and Europe.

We are advocating for our patients and their family members. This is an important product that will be an essential tool, not replaceable by PCC or aPCC products in the subset of major bleeds presenting to our ER departments while on a FXa inhibitor.

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.

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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: • Dr. Zafar Ahmad • Dr. Thomas Campbell • Dr. Daniel Shogilev • Dr. Brent Andruko		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Dr. Indy Ghosh*
Position	*ER Physician; Chair, Journal Club*
Date	*Please add the date form was completed (DD-MM-YYYY)06-09-2023*
☒	**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				
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	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name: Astra Zeneca	☒	☐	☐	☐
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				
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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				
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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.

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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.

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Add company name	☐	☐	☐	☐
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Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	ST0772-000-000
Brand name (generic)	Andexanet Alpha
Indication(s)	For adult patients treated with FXa inhibitors (rivaroxaban or apixaban) when rapid reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.
Organization	Dalhousie Emergency medicine group
Contact information[a]	Name: Sam G. Campbell

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.

I was surprised at the decision from CADTH to not recommend the reimbursement of this andexanet alpha in Canada. We are seeing more and more patients on DOACS every day. Life threatening bleeds are quite uncommon (especially those for which the outcome is not already declared), but on the occasion where they do occur, an effective antidote, given rapidly, offers the patient the best chance of recovery.

The panel is correct in saying that PCC is often used in these circumstances, but I disagree that it should be considered 'standard of care', in that evidence for PCC in these cases is sparse, and it is usually used as a 'Hail Mary' intervention when caregivers are desperate to do anything that might offer any possible hope of help to the patient, no matter how remote. As also noted by the panel, this use remains 'off label' for this indication, while that of andexanat alpha is 'on label'! While I concur that clinical data for andexanet alpha is limited to observational trials of sub-optimal quality, this limited evidence does suggest an advantage over PCC; furthermore, there is evidence that andexanet restores levels of Factor Xa to practically the same levels as in untreated patients within minutes.

Considering that we have an antidote that acts rapidly to directly restore activity of the clotting factor that the DOAC inhibits, and that what limited clinical data exists suggests a benefit over PCC (that is not even approved for this use), and considering that frontline caregivers have little faith in PCC as an effective option for DOAC related bleeds, I hope the panel will reconsider their recommendation to withhold reimbursement of andexanet alpha in Canada.

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?

I could not find input from Emergency Medicine apart form reference to a Journal club in EM from the Peel region, and some reference that emergency specialists would be comfortable in using the drug in consultation with a hematologist.

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. I believe the economic evaluation used comparators that are neither approved for the indication in question, nor are their use supported by evidence.		

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

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	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

New or Updated Declaration for Clinician 1	
Name	*Sam G. Campbell*
Position	*Professor of Emergency Medicine, Dalhousie University.*
Date	*31 August 2023*
☒	**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

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Astra Zeneca	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

C. New or Updated Conflict of Interest Declarations

30 August 2023

To: CADTH Andaxanet Alpha Reimbursement panel.

Re: decision to recommend not reimbursing for the use of andexanet alpha in Canada.

Dear Panel

I was surprised at the decision from CADTH to not recommend the reimbursement of this andexanet alpha in Canada. We are seeing more and more patients on DOACS every day. Life threatening bleeds are quite uncommon (especially those for which the outcome is not already declared), but on the occasion where they do occur, an effective antidote, given rapidly, offers the patient the best chance of recovery.

The panel is correct in saying that PCC is often used in these circumstances, but I disagree that it should be considered 'standard of care', in that evidence for PCC in these cases is sparse, and it is usually used as a 'Hail Mary' intervention when caregivers are desperate to do anything that might offer any possible hope of help to the patient. As also noted by the panel, this use remains 'off label' for this indication, while that of andexanat alpha is 'on label'! While I concur that clinical data for andexanet alpha is limited to observational trials of sub-optimal quality, this limited evidence does suggest an advantage over PCC; furthermore, there is evidence that andexanet restores levels of Factor Xa to practically the same levels as in untreated patients within minutes.

Considering that we have an antidote that acts rapidly to directly restore activity of the clotting factor that the DOAC inhibits, and that what limited clinical data exists suggests a benefit over PCC (that is not even approved for this use), and considering that frontline caregivers have little faith in PCC as an effective option for DOAC related bleeds, I hope the panel will reconsider their recommendation to withhold reimbursement of andexanet alpha in Canada.

Sincerely

Samuel G Campbell

MB BCh, CCFP(EM), FCFP, Dip PEC(SA), FCCHL, FRCP(Edin).

Research Director, Charles V Keating Emergency and Trauma Centre Queen Elizabeth II HSC, Halifax, Nova Scotia.

Professor of Emergency Medicine, Dalhousie University.

Halifax, Nova Scotia, Canada.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	ST0772
Brand name (generic)	Ondexxya (Andexanet alfa)
Indication(s)	Ondexxya (andexanet alfa) is indicated for adult patients treated with FXa inhibitors (rivaroxaban or apixaban) when rapid reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.
Organization	McMaster University Academic Faculty, Hematology/Thromboembolism
Contact information[a]	Dr. James Douketis (on behalf of group), [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. **Please see attached letter.**		

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? **Please see attached letter.**		

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	*McMaster University Academic Faculty, Dept. of Medicine, Div. of Hematology/Thromboembolism*
Position	*Faculty Members at Asst., Assoc., Full Professor Rank*
Date	*31-08-2023*
☒	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	☐
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	☐	☐	☐	☐

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: • Dr. James Douketis • Dr. Alfonso Iorio • Dr. Rick Ikesaka • Dr. Lori Ann Linkins • Dr. Siraj Mithoowani		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Dr. Alfonso Iorio*
Position	*Professor of Medicine, McMaster University*
Date	*30/08/2023*

☒	**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	*Dr. James Douketis*
Position	*Professor, McMaster University, Past-president, Thrombosis Canada*
Date	*30/08/2023*
☒	**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. Rick Ikesaka*
Position	*Assistant Professor, McMaster University*
Date	*30-08-2023*
☒	**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	*Dr. Lori Ann Linkins*
Position	*Associate Professor, McMaster University*
Date	*29-08-2023*
☒	**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	*Dr. Siraj Mithoowani*
Position	*Assistant Professor, McMaster University*
Date	*29-08-2023*
☒	**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	☐	☐	☐	☐

To: CADTH Reimbursement Review Committee

We are clinician-scientists in the Department of Medicine, Division of Hematology and Thromboembolism, at McMaster University and have reviewed the CADTH recommendations in regard to andexnet-a. Based on our review, we urge the Committee to re-consider their decision to not provide reimbursement for andexanet-a. This is based on the following considerations:

First, the Committee makes two pivotal points for their decision to not reimburse the drug for clinical use that raise concerns about the validity of this decision. These points are as follows:

1. ***"CPEC considered that the submitted evidence did not sufficiently demonstrate comparable therapeutic effects of andexanet alfa relative to prothrombin complex concentrate (PCC), which is the current standard of care."***

2. ***"However, it is uncertain whether the observed effects* (of andexanet) *could be attributed to andexanet alfa due to the absence of a control group."***

In regard to **Point 1**, that PCC is the "*current standard of care*", this is misleading and wholly inaccurate. PCC became the *de facto* agent to manage DOAC-associated bleeds when there were no other alternatives that specifically targeted DOACs for reversal. PCC cannot be regarded as a standard of care, as this implies that they have been rigorously evaluated and/or are supported in their use by strong recommendations from practice guideline groups. Neither of these criteria have been satisfied for PCCs. Acknowledging PCCs as the current standard of care is an example where 'practice is driving evidence' where our aim as clinician-scientists is the reverse, namely where 'evidence drives practice'.

When idarucizumab was investigated for reversal of dabigatran in the case of life-threatening bleeding, this drug was approved for clinical use and reimbursed by CADTH because it offered a specific alternative to PCC to rapidly eliminate the anticoagulant effect of dabigatran and, in fact, was the logical treatment option (often first-line) for rapid dabigatran reversal, leading to a decline in PCC use for dabigatran-associated bleeding. However, the same logic has not been applied to andexanet. Overall, there is no established first-line "standard of care" for DOAC reversal, but there should be options: to reverse dabigatran, the options comprise idarucizumab and PCC; to reverse oral factor Xa inhibitors, the options comprise andexanet and PCC. Patients who are receiving a DOAC and suffer a life-threatening should have access to all of these treatment options.

In regard to **Point 2**, that studies investigating andexanet are limited because of the "*absence of a control group"* creates an unfair double standard when one considers that both idarucizumab and PCC have been approved and are reimbursed even though the studies investigating these agents for DOAC reversal are also all uncontrolled studies similar to those of andexanet. There are no randomized trials comparing (a) PCCs to FFP, (b) PPCs to idarucizumab, (c) PCCs to andexanet (though such trials are in progress).

Second, CADTH does not consider the biological plausibility that PCC are not a targeted reversal agent for DOACs as this the case with dabigatran and andexanet. Indeed, the premise that PCCs should work at a biological level is not logical since there is no induced deficiency in coagulation

factors II, VII, IX and X when DOACs are administered and, in the case of life-threatening bleeding it does not make sense to administer additional clotting factors (PCC) to supraphysiologic levels rather than administer a targeted agent (idarucizumab or andexanet). Indeed, it is logical to administer PCCs for warfarin (or other VKA) life-threatening bleeds to target the diminished vitamin K-dependent levels. Overall, just as it is illogical to administer idarucizumab or andexanet for VKA-related bleeding one can similarly argue that it is illogical to give PCCs for DOAC-related bleeding.

Third, in the clinical domain of anticoagulant-related bleeding, clinicians and patients deserve treatment options, especially as there is no established standard of care. This is especially true for life-threatening and any significant intracranial bleeding where the margin for clinical error is reduced. Moreover, since life-threatening/intracranial DOAC-associated bleeding constitute only a minority of all DOAC-related bleeding it is established that specific DOAC reversal agents will not be widely used; indeed, their use should be restricted to a small proportion of patients in whom there is the potential for therapeutic benefit. Consequently, it makes little clinical sense that DOAC-specific reversal agents are not approved and reimbursed when their availability can **(a)** offer clinicians and patients a targeted therapeutic option, and **(b)** is unlikely to result in widespread use and associated strain on health care resources.

Based on these factors, we urge CADTH to reconsider their decision on reimbursement for andexanet so as to given clinicians an important treatment option and, more importantly, to allow patients to have access to a potentially life-altering treatment option.

Sincerely yours,

[redacted]

James Douketis MD, FRCPC, FCAHS
Professor and David Braley-Nancy Gordon Chair in Thromboembolic Disease
Department of Medicine, McMaster University
Past-President, Thrombosis Canada (www.thrombosiscanada.ca)

[redacted]

Dr. Rick Ikesaka MD, MSc, FRCP
Assistant Professor
Department of Medicine, McMaster University

Siraj Mithoowani MD, FRCPC
Assistant Professor
Department of Medicine, McMaster University

[redacted]

Lori-Ann Linkins MD, FRCPC, MSc
Associate Professor
Department of Medicine, McMaster University

[redacted]

Dr. Alfonso Iorio MD, PhD, FRCPC
Professor, Department of Medicine, McMaster University
Chair, Department of Evidence, Impact and Research

Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	ST0772
Name of the drug and Indication(s)	Andexanet Alfa (Ondexxya) for reversal of anticoagulation
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	☐
	No requested revisions	X☐

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.

Version: 1.0
Publication Date: TBC
Report Length: 2 Pages

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.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	ST0772
Brand name (generic)	Ondexxya (Andexanet alfa)
Indication(s)	Ondexxya (andexanet alfa) is indicated for adult patients treated with FXa inhibitors (rivaroxaban or apixaban) when rapid reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.
Organization	Members of CanVECTOR
Contact information[a]	Names: Carol West, Suzanne Dubois

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).

We do not agree with the committee's recommendation.

As patients and caregivers who are prescribed DOACs to manage the risk of VTE we are disheartened by the decision not to recommend reimbursement for this medication that has the potential to save many lives. It is our understanding that andexanet alpha has been approved and used in more than ten other nations for over a decade—these countries obviously find that there is a benefit to its use in situations where patients on DOACs experience life-threatening bleeding. We feel that the comparison to the "current standard of care" with 4FPCC is not logical, since we understand that its use is "off label" for this purpose, and so should not be seen as a comparable therapy. We are also concerned that the decision not to recommend reimbursement does not adequately address the concerns and preferences of patients as stated in the "Patient Group Input" section of this report, as "patients expressed that bleeding is the most concerning potential side effect of VTE treatments…", and "the lack of a reversal agent was mentioned as a concern by a few patients". We would like to point out that this was mentioned by a "few" patients who were not asked directly about reversal agents—we are confident that most patients on DOACs would respond that this is of great concern.

DOACs are the preferred choice for treating many conditions where blood clotting is a concern, and the rates of DOAC use are only going to increase as our population ages. Furthermore, many patients on DOACs are younger (many not yet adults), and they deserve to have access to this potentially life-saving medication. With increased use of DOACs comes increased situations where there are challenges in controlling life-threatening bleeding. These patients should not be given off-label therapies to control dangerous bleeding when there is a more effective alternative: andexanet alpha.

Expert committee consideration of the stakeholder input		
	Yes	☒

2.Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	No	☒

(If not, what aspects are missing from the draft recommendation?)

To be fair, some of the patient input was taken into consideration. However, we do believe that the reasons for the recommendation are limited and do not justify the negative response. This is a question of treatment which should rely heavily on the experience of patients. For example, one of the main concerns of patients is reversal for prevention of bleeding with urgent surgery, and this was considered outside of scope since the submission was related to treatment/reversal of a bleeding event.

Clarity of the draft recommendation

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

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

Unfortunately, the request for approval was not able to be supported by strong research evidence. In the absence of this, we regret that there is no flexibility for provisional approval of funding for a period of time (say, 3-5 years) with close monitoring of effectiveness of clinical use. It is not so much that clarification is required, but that consideration be given to an innovative approach in this instance, given the potentially life-threatening consequences if andexanet alpha is not available.

3. 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).

Once again, we believe the analysis has been limited. As pointed out above, a number of countries support the use of this product. This decision is out of step with Canada's commitment to harmonization and standardization of care across borders, with consistent availability of the best care for patients.

Also, it restricts patient choice within Canada, taking an option for care out of the patient's hands.

4. 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.

Not applicable

[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	*Carol West, Suzanne Dubois*
Position	*Members of CanVECTOR*
Date	*31/08/2023*
☒	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	☐
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	ST0772
Brand name (generic)	Ondexxya (Andexanet alfa)
Indication(s)	Ondexxya (andexanet alfa) is indicated for adult patients treated with FXa inhibitors (rivaroxaban or apixaban) when rapid reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.
Organization	Thrombosis Canada
Contact information[a]	Name: David Airdrie & Deborah Siegal on behalf of Thrombosis Canada

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

On behalf of Thrombosis Canada, I (Deborah Siegal, MD) am writing to request that CADTH reconsider the decision to not provide reimbursement for andexanet alfa for the treatment of severe/life-threatening bleeding in patients taking oral factor Xa inhibitor anticoagulants.

As a hematologist (thrombosis medicine) with clinical and research expertise in anticoagulant-related bleeding, I would like to emphasize that bleeding is the main complication of anticoagulant therapy that leads to a **high risk of death and disability with limited specific treatment options available.** Oral anticoagulants (OACs), including factor Xa inhibitors, are prescribed to prevent and treat cardiovascular diseases such as stroke and venous thromboembolism (VTE). More than 40 million prescriptions for OACs are written annually in North America, including over 7 million in Canada (as of 2014) and factor Xa inhibitors have become the most prescribed OAC. **Given population aging and expanding indications for OAC treatment, anticoagulant-related bleeding is expected to become an even greater health problem within Canada and worldwide.**

Patients with serious anticoagulant-related bleeding have a high-risk of death and disability. Therefore, bleeding cessation is a clinical priority. About 2% to 4% of patients receiving OACs experience major bleeding annually, and another 10% experience clinically relevant non-major bleeding. Major bleeding complications increase the short-term risk of death by 35-fold for intracranial bleeding and 5-fold for extracranial bleeding. Patients with OAC-related major bleeding have **30-day mortality rates up to ~10% to 40%** (depending on the site of bleeding) emphasizing the need for management strategies to improve outcomes. In a survey of Canadians receiving OAC treatment, 75% of respondents indicated they would feel more comfortable taking an anticoagulant if they knew a reversal agent was available for treating major bleeding. **Patients and physicians ought to have treatment choices when faced with treatment-related complications that have severe adverse outcomes, particularly in the absence of an established standard of care treatment (which PCC is not - see below).**

Reversal of anticoagulant effect is an important component of managing severe bleeding on anticoagulants. **Reversal agents should be used judiciously** in conjunction with maximum supportive measures, referral for definitive interventions, and post-bleed assessments for anticoagulant resumption to mitigate thrombotic risk. Instead of limiting the availability of treatments for everyone (as is the outcome of the CPEC recommendation), ensuring that protocols and mechanisms are in place could limit the use of reversal agents for patients most likely to benefit, in keeping with the principles of stewardship. **Unlike**

warfarin and dabigatran for which reversal strategies are approved and reimbursed, there are currently no reversal agents for factor Xa inhibitor anticoagulants.

Discussion Point #1: "*CPEC considered that the submitted evidence did not sufficiently demonstrate comparable therapeutic effects of andexanet alfa relative to prothrombin complex concentrate (PCC), which is the current standard of care*".

PCC is not an established "standard of care" treatment based on studies showing an effect on clinical outcomes or biochemical markers. PCC has been used by physicians in clinical practice (without evidence) in the absence of other options for treatment of patients with factor Xa inhibitor related bleeding patients at high risk of severe outcomes. Unlike warfarin reversal, PCC has not been shown definitively to "reverse" anticoagulant effect, nor it is there convincingly evidence of enhanced clinical or laboratory hemostasis in the setting of factor Xa inhibitor anticoagulants. Although it has been proposed to "overcome anticoagulant effect" by supplying exogenous vitamin K dependent coagulation factors, this proposed mechanism has not been proven and the plausibility of this mechanism is highly questionable given factor Xa inhibitor anticoagulants inhibit anticoagulation at late stages of the coagulation cascade. Further, there is no established dose of PCC in this setting with doses ranging from 2000 units fixed dose to 50 units/kg further (maximum dose or no maximum dose) highlighting the inconsistencies of existing data and uncertainty about effect. As a result of these considerations, recommendations from the **National Advisory Council on Blood and Blood Products** states the following regarding the treatment of bleeding in patients receiving direct factor Xa inhibitor anticoagulants:

- PCCs should only be considered in patients presenting with severe or life-threatening bleeding.
- **Specific reversal agents for direct factor Xa inhibitors (including rivaroxaban, apixaban, and edoxaban), such as andexanet alfa, should be used, if available**. At the time of writing, andexanet alfa is not currently approved by Health Canada.
- There are no randomized trials published as of writing, evaluating the efficacy and safety of PCCs for treatment of direct factor Xa inhibitor associated bleeding.
- The optimal dosing strategy is uncertain with 2000 IU (fixed dose) or 25-50 IU/kg (to a max 3000 IU) being the most commonly recommended dosing strategy.

In fact, the data regarding effectiveness and safety of PCC are derived primarily from retrospective cohort studies of patients treated in routine clinical practice without control groups. These patients were not required to consent to study procedures and there were no standardized protocols in place with respect to eligibility, dosing, clinical assessments, imaging, laboratory testing, follow-up, etc. As a result, these studies are likely subject to significant bias and confounding that cannot be ignored. So, it seems highly contradictory to recommend a non-specific treatment based on data that is, arguably, more methodologically flawed and uncertain than a single arm prospective study conducted as a registered trial protocol and developed in discussions with regulatory authorities.

Discussion Point #2: *"It is uncertain whether the observed effects (of andexanet) could be attributed to andexanet alfa due to the absence of a control group"*.

As discussed above, clinical evaluations of PCC, endorsed by CPEC as the "standard of care", also do not include control groups. Similarly, idarucizumab (a monoclonal antibody for reversal of dabigatran) was approved and is reimbursed based on the registration trial REVERSE-AD which was a prospective single-arm study of dabigatran-treated patients with major bleeding or requiring urgent surgery which included similar hemostatic efficacy and biochemical endpoints as those in the ANNEXA-4 study. This represents a lack of consistency among recommendations for similar treatments based on data with similar methodological issues.

Discussion Point #3: *"CPEC considered the input by the clinical experts consulted by CADTH that the treatment effects of andexanet alfa were consistent with the clinical experts' clinical experience with PCC".*

The emphasis on "clinical experience" undermines the credibility of the evidence review process which aims to provide Canadian patients and physicians with treatments based on the best available evidence, while acknowledging its limitations. As the first point listed in the "Discussion Points" section of the recommendation document, this summary assessment is suboptimal at best and problematic at worst. Given that clinicians in Canada have no clinical experience with andexanet, the added value of this input is not clear. This emphasizes the miscategorization of PCC as the "standard of care" treatment in this setting.

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	☒
In addition to the above, there was no mention of the patient feedback that we submitted that patients would be more comfortable taking an anticoagulant knowing that there was a reversal agent available in the case of a major bleed.		

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	
Position	
Date	
☐	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	☐	☐	☐	☐

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: • Dr. Deborah Siegal, Secretary, Thrombosis Canada		

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	
Position	
Date	
☐	**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	☐	☐	☐	☐