CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

berotralstat (Orladeyo)

(BioCryst Pharmaceuticals Inc.)

Indication: hereditary angioedema (HAE)

February 3, 2023

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0723-000
Brand name (generic)	Orladeyo (Berotralstat)
Indication(s)	Hereditary angioedema (HAE)
Organization	Canadian Hereditary Angioedema Network (CHAEN)
Contact information[a]	Name: Peter Waite, Executive Director Canadian Hereditary Angioedema Network [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.

CHAEN agrees with the revised recommendation where CDEC determined that the clinical relevance of the reduction in frequency of attacks from 2.35 attacks per month in the placebo group to 1.31 attacks in the berotralstat group was statistically significant and clinically relevant.

CHAEN also acknowledges that upon reconsideration, CDEC carefully considered that HRQoL data from the APeX-2 trial did not reflect the need for both a non-plasma derived and oral option for preventing HAE, and that CDEC respected patient and clinician group feedback with respect to QoL issues associated with route of administration.

CHAEN agrees that berotralstat should not be used in combination with other long-term prophylactic treatment of angioedema (e.g., C1-esterase inhibitors or lanadelumab), however, consideration needs to be given to how patients are transitioned to berotralstat.

"However, the optimal approach for switching a patient to oral berotralstat prophylaxis has not been defined. Factors to consider include the timing of the transition, the half-life of the medications, the dosing schedules for both drugs, and patient-specific characteristics that may affect the transition." *

The International/CHAEN HAE Guideline (Betschel et al. Allergy Asthma Clin Immunol 2019) with respect to starting LTP treatments states that decisions with respect to how a patient transitions to berotralstat should be made by the patient and an HAE specialist.

Additionally, we also suggest that patients on berotralstat should have the opportunity, where necessary, to use C1 inhibitor as short-term prophylaxis before known triggers such as surgery, dental work, etc., as recommended by their HAE specialist.

*Gower, R.G., Wilber, M. Considerations for transition from subcutaneous to oral prophylaxis in the treatment of hereditary angioedema. Allergy Asthma Clin Immunol 17, 100 (2021). https://doi.org/10.1186/s13223-021-00603-9

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.

ICER

On p. 4 in Table 1 (Reimbursement Conditions and Reasons). There is a pricing recommendation:

> *The ICER for berotralstat is $14,559,490 when compared with No LTP.*
>
> *A price reduction of 93% would be required for berotralstat to be able to achieve an ICER of $50,000 per QALY compared to No LTP.*

CHAEN represents expert clinicians with expert knowledge of the clinical factors related to the treatment of HAE, and we typically do not delve into the economic aspects of a Health Technology Assessment.

However, we are concerned that CADTH's recent use of an ICER pegged at $50,000 per QALY as the willingness-to-pay (WTP) threshold for payers is not will aligned with the unique needs of rare diseases, and favors treatments for more common diseases.

We support the work of Canadian health technology assessment agencies and the pan Canadian Pharmaceutical Alliance (pCPA) in assessing value and achieving value in prescription medications for publicly funded drug programs. However, we are concerned that CADTH is arbitrarily establishing a new (and low) WTP threshold that could ultimately result in Canadian patients with rare diseases being denied access to important new therapies.

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.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.
Conflict of Interest Declaration	

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0723
Name of the drug and Indication(s)	Berotralstat (Orladeyo) for hereditary angioedema (HAE)
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.
c) Implementation guidance
Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0723-000
Brand name (generic)	Orladeyo (Berotralstat)
Indication(s)	hereditary angioedema (HAE)
Organization	Hereditary Angioedema Canada (HAEC)
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.

HAEC agrees with the revised recommendation that importantly recognizes the clinical relevance of the reduction in frequency of attacks demonstrated in the APeX-2 trial. HAEC also acknowledges the dutiful consideration CDEC gave to stakeholder feedback on the draft 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	☐

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

Re: Table 1. Reimbursement Conditions and Reasons

Prescribing:

Berotralstat should not be used in combination with other medications used for long-term prophylactic treatment of angioedema (e.g., C1-esterase inhibitors or lanadelumab).

While HAEC agrees with CDEC that berotralstat should not be used in combination with other long-term prophylactic treatment of angioedema, consideration needs to be given on how a patient transitions to berotralstat.

"However, the optimal approach for switching a patient to oral berotralstat prophylaxis has not been defined. Factors to consider include the timing of the transition, the half-life of the medications, the dosing schedules for both drugs, and patient-specific characteristics that may affect the transition."[1] In concordance with The International/Canadian Hereditary Angioedema Guideline (Betschel et al. Allergy Asthma Clin Immunol 2019) with respect to starting LTP treatments, we believe decisions with respect to how a patient transitions to Berotralstat should be made by the patient and an HAE specialist. We also suggest that patients on Berotralstat should have the opportunity, if necessary, to use C1 inhibitor as short-term prophylaxis before known triggers such as surgery, dental work, etc., as recommended by their HAE specialist.

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.

[1] Gower, R.G., Wilber, M. Considerations for transition from subcutaneous to oral prophylaxis in the treatment of hereditary angioedema. *Allergy Asthma Clin Immunol* **17**, 100 (2021). https://doi.org/10.1186/s13223-021-00603-9

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	*Jacquie Badiou, on behalf of the HAEC Advocacy Committee*
Position	*Chair of Advocacy Committee and HAEC Past President*
Date	*February 2, 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 Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0723-000
Brand name (generic)	Orladeyo® (berotralstat)
Indication(s)	HAE
Organization	BioCryst Pharmaceuticals Inc.
Contact information[a]	[redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
BioCryst Pharmaceuticals Inc. appreciates CADTH's recommendation to "Reimburse with Conditions" for Orladeyo® (berotralstat). This recommendation is an important step for patients with hereditary angioedema (HAE). Orladeyo® is the first and only targeted orally administered treatment that can be used for the routine prevention of HAE in adults and pediatric patients 12 years of age and older. As a Health Canada approved, efficacious, and well-tolerated oral long-term prophylactic option, it meets an important unmet need for patients with HAE 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	☐
Not applicable.		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
Not applicable.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
Not applicable.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
Not applicable.		

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