CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

RAVULIZUMAB (Ultomiris)

(Alexion Pharma Canada Corp.)

Indication: For the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

January 27, 2022

CADTH

CADTH Reimbursement Review Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	
Brand name (generic)	**ravulizumab**
Indication(s)	PNH
Organization	London Health Sciences Centre
Contact information[a]	Name:Ian Chin-Yee

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. Overall supportive of the recommendations for using Ravi and Ecu interchangeably. Kudos to CADTH although for treaters of PNH and patients this has been long time coming. Appreciate the apparent flexibility in timing dosing in those patients with breakthrough hemolysis with allowance for clinical empiric trial in a given patient. I would consider switching to Ravi q 8 weeks to start if patient was having breakthrough with ECU q 2 weeks before trying any shorter interval Ecu or Ravi. Patient factors such as IV access and convenience provide out patients with alternative assuming cost equivalence. Recognize that Ravi is also IV but even 1 to 3 less pokes would be huge factor for many patients with poor IV access.		

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. Use in pregnancy?		
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.		

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

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Please state full name Ian Chin-Yee*
Position	*Please state currently held position Hematologist Professor of Medicine Western University of Ontario*
Date	*Please add the date form was completed (26-01-2022)*
☒	**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. NONE IN PAST 2 YEARS				
None in past 2 years	**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	*Ian Chin-Yee*
Position	*Hematologist, Program Head Laboratory Medicine*
Date	*Please add the date form was completed (01-02-2022)*
☒	**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.				
None in past 2 years	**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	SR0700
Name of the drug and Indication(s)	Ravulizumab (Ultomiris) for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH)
Organization Providing Feedback	FWG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	X
	No requested revisions	☐

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
b) Reimbursement conditions and related reasons
c) Implementation guidance

CADTH

CADTH Reimbursement Review Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0700-000
Brand name (generic)	Ultomiris (ravulizumab)
Indication(s)	Paroxysmal Nocturnal Hemoglobinuria (PNH)
Organization	Alexion Pharma Canada Corp
Contact information[a]	[redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
The Sponsor (Alexion AZ) agrees with the committee's draft recommendation to list with conditions and is pleased that the clinical and economic value of Ultomiris (ravulizumab) to treat the majority of PNH patients is recognized by CADTH. Alexion AZ looks forward to working with pCPA and jurisdictions to discuss funding of Ultomiris for PNH patients		

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	☐
The sponsor appreciated the committee recognition of the patient input outlining the quality of life benefit Ultomiris (ravulizumab) will have on managing their PNH for extended periods of time which allows patients the freedom to enjoy life.		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
Yes, the reasons for the recommendation is clearly stated by the committee.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
Yes, the committee has provided clear guidance for implementation in stating: "Patients already receiving eculizumab treatment with adequate treatment response should be eligible to directly switch to ravulizumab treatment without having to meet the initiation criteria".		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
The sponsor would like to recommend to the committee that condition # 2 (under initiation) *"Patients with insufficient initial response or who have failed treatment with eculizumab at the Health Canada recommended dosage are not eligible for reimbursement of ravulizumab"* should be deferred to clinical experts who treat PNH, to determine whether a patient should be eligible for a treatment switch from eculizumab to ravulizumab. In doing so, clinical experts are empowered to make an informed decision to offer a personalized therapeutic approach, rather than utilizing a one-size-fits-all model.		

The clinical data in the submission are clear with respect to breakthrough hemolysis (BTH) arising from incomplete C5 inhibition, in that it is rare with ravulizumab because the C5 inhibition is immediate, complete, and sustained compared with eculizumab due to tailored weight-based dosing and long-acting formulation.

In clinical studies, patient-level data were evaluated in detail to assess causes and clinical parameters associated with incidents of BTH reported during the 26-week treatment periods in the ravulizumab phase 3 PNH studies (ALXN1210-PNH-301; ALXN1210-PNH302). Of the five BTH events occurring in ravulizumab-treated patients across the studies, none were temporally associated with suboptimal C5 inhibition (free C5 ≥0.5 µg/mL); four (80.0%) were temporally associated with complement-amplifying conditions (CACs). Of the 22 events occurring in eculizumab-treated patients, eleven were temporally associated with suboptimal C5 inhibition, including three events also associated with concomitant infection. Six events were associated with CACs only. Five events were unrelated to free C5 elevation or reported CACs. Patients in 301 who experienced BTH due to incomplete C5 inhibition on eculizumab, after switching to ravulizumab in the extension period did not experience any BTH due to incomplete C5 inhibition.

These results suggest that the immediate, complete, and sustained C5 inhibition achieved with ravulizumab, reduces the risk of BTH by eliminating BTH arising from suboptimal C5 inhibition in patients with PNH. Moreover, ravulizumab offers a personalized approach through a weight-based dosing regimen to ensure that all patients receive an appropriate dose of complement inhibitor. Based on the information above, we believe that the clinical experts should be empowered to switch patients from eculizumab to ravulizumab, in any clinical scenario, where they believe that ravulizumab may be more beneficial for the patient. This recommendation offers flexibility to clinicians treating PNH patients, while maintaining cost neutrality.

Table 19: Breakthrough Hemolysis

Breakthrough hemolysis	Study 301 Ravulizumab N = 125	Study 301 Eculizumab N = 121	Study 302 Ravulizumab N = 97	Study 302 Eculizumab N = 98
Patients with breakthrough hemolysis, n (%)	5 (4.0)	13 (10.7)	0	5 (5.1)
Mean difference, % (95% CI)	−6.7 (−14.21, 0.18) P = 0.0558	REF	−5.1 (−18.99, 8.89)	REF
Breakthrough hemolysis events, n	5	15	0	7
Free C5 > 0.5 µg/mL alone	0	5	0	3
Complement amplifying condition (i.e., infection) alone	4	4	0	2
Free C5 ≥ 0.5 µg/mL and concomitant infection	0	2	0	1
Undetermined*	1	4	0	1

CI = confidence interval; NA = not applicable; REF = reference group

Source: Clinical study reports for Studies 301 and 302 [R,N]

NOTE: Patients with breakthrough hemolysis, evaluated in the full analysis set, were those with > 1 worsening symptom or sign of intravascular hemolysis in the presence of LDH of ≥ 2 × ULN following prior reduction of LDH to < 1.5 ×ULN. In accordance with the closed testing procedures, the outcome was tested for noninferiority in both studies and for superiority in Study 301. Difference in percentage of patients with breakthrough hemolysis was calculated as a weighted combination of differences in each randomization stratum using Mantel-Haenszel weights. The 95% CI was computed using the stratified Newcombe CI method

*Undetermined breakthrough hemolysis events were those without free C5 ≥ 0.5 µg/mL and without an identified concomitant infection

[References are the following:

- Clinical Study Report: ALXN1210-PNH-301. A phase 3, randomized, open-label, active-controlled study of ALXN1210 versus eculizumab in complement inhibitor-naïve adult patients with paroxysmal nocturnal hemoglobinuria (PNH) [internal sponsor's report]. New Haven (CT): Alexion Pharmaceuticals, Inc.; 2018.
- Clinical Study Report: ALXN1210-PNH-302. A phase 3, randomized, open-label, active-controlled study of ALXN1210 versus eculizumab in adult patients with paroxysmal nocturnal hemoglobinuria (PNH) currently treated with eculizumab [internal sponsor's report]. New Haven (CT): Alexion Pharmaceuticals, Inc.; 2018.

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