CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

ravulizumab (Ultomiris)

(Alexion Pharma GmBH)

Indication: For the treatment of adult and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).

December 1, 2022

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0740-000
Brand name (generic)	Ultomiris
Indication(s)	Atypical Hemolytic Uremic Syndrome
Organization	Calgary Apheresis Group
Contact information[a]	Name: Dr. Louis Girard

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 agree with this recommendation as written. Ravulizuab appears to be as clinically efficacious as eculizumab. This will enable patients with aHUS to be able to access anti-complement therapy as equitably as patients with PNH, which was not the case with eculizumab. Additionally, this will result a substantial cost benefit (~33% reduction) compared with eculizumab. This is an important step forward for this costly medication.		

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐
If not, what aspects are missing from the draft recommendation?		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

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

Appendix 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	*Dr. Louis Girard*
Position	*Nephrologist & Clinical Professor of Medicine; University of Calgary*
Date	*2022/NOV/30*
☒	**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**
Alexion	☐	☒	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Dr. Kim Cheema*
Position	*Nephrologist & Clinical Assistant Professor; University of Calgary*
Date	*2022/NOV/30*
☒	**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**
Alexion	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Dr. Jeffrey Ma*
Position	*Nephrologist & Clinical Assistant Professor; University of Calgary*
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**
Alexion	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Dr. Davinder Sidhu*
Position	*General Pathologist, Transfusion Medicine and Associate Professor*
Date	*2022/NOV/30*
☒	**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**
Alexion	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0740
Name of the drug and Indication(s)	Ravulizumab (Ultomiris) for adult and pediatric patients with atypical hemolytic uremic syndrome
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	X
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	
	No requested revisions	☐

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification.
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification. • Reimbursement condition 1.1 - Could the stipulation that TMA must be unexplained (i.e. not a secondary TMA) be stated with the aHUS definition here, rather than in 1.2.i (as this should apply to all patients requesting reimbursement)?

Version: 1.0
Publication Date: November 2022
Report Length: 3 Pages

- 1.1.ii – Should STEC testing be required for all patients, or just those with a history of bloody diarrhea in the past 2 weeks (as in ON's eculizumab criteria)?
- 1.2 – Request clarified criteria wording to indicate that plasmapheresis should only be a prerequisite "if appropriate". This would be in keeping with the implementation guidance stating plasmapheresis is not recommended in certain settings.
- 1.2. – Is there any flexibility on the number of plasma exchange sessions/days that need to be attempted? This may depend on individual clinical circumstances.
- 1.3.i c) – Suggest the following wording clarification: "SCr > the age appropriate ULN in pediatric patients (~~subject to advice from~~ *as determined by or in consultation with* a pediatric nephrologist)".
- 2. – To exclude transplant patients with a history of secondary TMA only, should this be revised from "history of TMA" to "history of aHUS"?
- 2. – Should it be noted here that patients should not have a history of ravulizumab treatment failure (in case it had been tried with a previous aHUS occurrence)?
- 2.1 – Is there any guidance on the definition of "immediately" in this context? E.g. within hours, or days?
- 2.1 – Should it be specified that post-transplant TMA must also not be secondary TMA?
- 2.2 – If a patient previously lost their native kidney to TMA/aHUS, and aHUS is now occurring in their transplanted kidney, such patients would not be included under this reimbursement condition. Should they be included, as their current graft is similarly at risk to a patient who's had a second, third, etc. transplant?
- 2.3 – If the intent here is that this would be a post-transplant aHUS prophylaxis regimen, can the wording more clearly reflect that? E.g "Have *history of* proven aHUS and require *prophylaxis with ravulizumab at the time of* a kidney transplant".
- 2.3 – Can an eligible timeline/duration for the prophylaxis be provided? E.g. start at the time of the transplant surgery and then a 6 month duration would be consistent with ON's eculizumab criteria in post-transplant prophylaxis.
- 3. – Should there be separate renewal criteria for the 6 month renewal than for the renewal(s) at month 12 and beyond, such as is in ON's eculizumab criteria? (e.g. the month 6 criteria ensures a treatment response and no treatment failure, and the month 12 criteria ensures both continued response and that rationale for continued treatment [generally limited organ reserve or high-risk genetic mutation] is present in that patient.)
- 3.1 – Can the other examples of favorable response outcomes noted in the "Reason" column be incorporated into criteria 3.1 as well? Additionally, are there any definitions of treatment failure that should NOT be met (as in ON's renewal criteria)?
- 3.2 – Overall treatment duration being determined per physician discretion is likely not feasible for the plans considering the cost of this drug. Could reimbursement condition 3.2 provide some direction, similar to ON's continuation criteria at 12 months? E.g. would the need for long-term funding be generally based on factors like limited organ reserve or high-risk genetic mutation?

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.

- It was noted that ravulizumab could be considered on a case-by-case basis for patients who do not respond or lost response to treatment with eculizumab. Is there further guidance on scenarios where this is likely to be appropriate?
- For the Implementation Guidance on circumstances for restarting drug:
    - For i), should the TMA definition align with that stated in reimbursement condition 1.2? (Perhaps minus the need for a plasmapheresis re-trial?)
    - For ii), is this already addressed in circumstance i)? That is, would this fall under preventing end organ damage (such as permanent ESKD) as the overall purpose of the treatment?

Could this be addressed with criteria? (See ON recommencement criteria).

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. In the reason column renewal section, it is noted that lifelong treatment may be considered for patients with high-risk complement genetic variations. Could the clinical experts provide specific examples of these high-risk genetic variations? 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 Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0740-000
Brand name (generic)	ravulizumab
Indication(s)	atypical Hemolytic Uremic Syndrome
Organization	aHUS Canada
Contact information[a]	Name: Michael Eygenraam

Stakeholder agreement with the draft recommendation		
1. **Does the stakeholder agree with the committee's recommendation.**	Yes	☑
	No	☐
We agree with the recommendation to "reimburse with conditions", however we believe some of the conditions could be improved as stated in below comments.		
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	☐
While CADTH included most of the critical points in our input, there were two key points that were missed. 1) In the "Patient Input" section of the Stakeholder Perspectives on page 9, the last paragraph should include "improved quality of life" as one of the common, patient-listed benefits. 2) The last sentence of that final paragraph left out an important patient perspective in our original input, without which it appears too negative. It should read, "While patients reported experiencing headache, nausea and body aches right after their infusion or during the month after the infusion, they said the overall benefits were worthwhile as these side effects were the same as or better than previous treatments."		
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	☑
We have two concerns requiring clarification. 1) We are not certain that the guidance information (column 3) on Table 1 will be included in the final conditions. If not included, we are concerned that valuable guidance will not be used. Whether included or not, we recommend that more guidance be written directly into the conditions (criteria) for clarity since the conditions as written do not adequately address all patient scenarios. Without more guidance written in the conditions, some aHUS patients with legitimate need will not obtain access to this treatment. 2) While there is some guidance on restarting ravulizumab in the second paragraph of Table 1's 3rd column, we believe it would be important to have this written directly in the conditions. It would be most clear if put under its own heading titled "Restarting"		

since it is not so applicable under the “Initiation” nor “Renewal” headings. Conditions allowing immediate access to ravulizumab should be made clear for cases where the diagnosis has previously been established and a relapse has occurred in this subset of aHUS patients who are off treatment. The guidance written beside the condition may then explain the immediate need of restarting due to the aggressive nature of aHUS and how it can damage organs within 24 – 48 hrs.

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

Generally we believe the conditions in Table 1 are a good starting point, however since the manifestation of aHUS symptoms varies greatly from patient to patient, the conditions as written may exclude some properly diagnosed patients who do not fit the explicit criteria given and some conditions may unnecessarily harm patients. Therefore, we suggest a few changes in the conditions:

1) Under condition 1.2, there is a minimum of 4 plasma exchanges required over 4 days. According to reference #6 in the first paragraph of the “Background” section, plasma exchange is not required to establish a diagnosis of aHUS, and so requiring plasma exchanges in the condition for reimbursement should not exist in the conditions. The use of plasma exchanges should be up to the discretion of the specialist physician. After an aHUS diagnosis and TMA are established, a specialist clinician would administer a C5 inhibitor immediately to reduce any chance of organ damage caused by the TMA, since plasma does not control organ damage in aHUS.
2) Why is the statement in condition 1.2.ii. part of the conditions? It is suggesting a possible biopsy to confirm TMA in patients who do not have evidence of platelet consumption and hemolysis. We do not see guidance defining its use. TMA is defined by hemolysis and platelet consumption as described in 1.2.i.. Was a biopsy included to catch a possible case where TMA is suspected and the blood work is inconclusive?
3) Additionally, in condition 1.2.ii. we suggest adding some guidance on the risk of uncontrolled bleeding from doing a biopsy on patients who have low platelet numbers.
4) In condition 1.3 it is suggested that there must be documented clinical evidence of organ impairment in the kidneys or brain. The CDEC and the clinical experts agree that aHUS may show impairment to any organ and is not limited to the kidneys and brain (see first sentence in “Background” section on page 8 and paragraph 3 of the “Clinician Input” on page 10). Why then do the conditions for reimbursement require evidence of impairment in one of those two organs only? If organ impairment was a necessary condition of reimbursing ravulizumab, the conditions under 1.3 of Table 1 should be opened up to any organ impairment, however this condition should be removed altogether. If a diagnosis of aHUS is established and TMA is present but organ damage has not yet occurred, why wait until organ damage occurs before reimbursing ravulizumab? This would unnecessarily harm some patients.

[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	*Michael Eygenraam*
Position	*Chair*
Date	*30-11-2022*
☑	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	SR0740-000
Brand name (generic)	Ultomiris (Ravulizumab)
Indication(s)	aHUS
Organization	Alexion Pharma GmbH
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 Pharma GmbH [Alexion]) 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 aHUS patients is recognized by CADTH and will provide substantial cost savings for the jurisdictions upon listing vs Soliris.
Alexion looks forward to working with pCPA and jurisdictions to expedite the listing of Ultomiris for aHUS patients and realize the substantial savings sooner for jurisdictions.

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

The sponsor appreciates the committee's acknowledgement that aHUS is a rare, life-threatening condition, for which there is variability in access to existing pharmacological therapy amongst public drug plans. Based on the natural history of disease without treatment, the committee concluded that there is an unmet need.
CADTH recognized the patient input outlining the quality of life benefit Ultomiris (Ravulizumab) will have on managing their aHUS for extended periods of time, reduced burden on treatment challenges 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 are clearly stated and reference multiple expert opinions who treat this life threatening and rare disease providing strong clinical validation to these recommendations by CADTH.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐

Yes, CADTH has provided clear guidance to stakeholders to treat aHUS defined by presence of TMA along with clarity around restarting treatment on a case by case basis, addressing transplantation clearly and testing for the pediatric population which differs from adults clearly demonstrate insights from expert clinical opinion.

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

CADTH clearly identified Ultomiris aHUS as meeting an unmet medical need in treating patients and have recommended jurisdictions to list at least equal or less than that of the comparator Soliris.

Based on CADTH reanalyses, the budget impact of reimbursing ravulizumab for the treatment of adult and pediatric patients with aHUS to inhibit complement-mediated TMA resulted in cost savings to the drug plans of $9,837,687 in year 1, $18,220,135 in year 2, and $21,453,528 in year 3, for a three-year total of $49,511,350.

Clearly there are substantial savings available to jurisdictions upon listing Ultomiris aHUS and as sponsor we are certainly willing to collaborate with pCPA and each jurisdiction to do so in an expedited manner to optimize savings for the jurisdictions.

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