CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

ravulizumab (Ultomiris)

(Alexion Pharma GmbH)

Indication: For the treatment of adult patients with anti-aquaporin 4 (AQP4) antibody-positive neuromyelitis optica spectrum disorder (NMOSD).

March 1, 2024

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0785
Name of the drug and Indication(s)	Ravulizumab (Ultomiris) for the treatment of adult patients with antiaquaporin 4 (AQP4) antibody-positive neuromyelitis optica spectrum disorder (NMOSD)
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	SR0785-000
Brand name (generic)	ULTOMIRIS (Ravulizumab)
Indication(s)	Neuromyelitis optica spectrum disorder (NMOSD)
Organization	MS Canada
Contact information	Name: Jennifer McDonell

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

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 recommendation appears to reflect the patient input however in the *implementation issues* section we note the CDEC comment on the lack of evidence to *define order of use*. MS Canada acknowledges this is based on a paucity of evidence between the agents however it is not clear if CDEC considered patient decision-making around administration, side effects, lifestyle, etc.

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

The majority of the reasons are clearly stated however clarity would be helpful in the following areas:
-switching from eculizumab to ravulizumab (individuals who are responding well to C5 inhibitors but want to reduce the frequency of administration, and reduce cost).
-switching from another NMOSD therapy to ravulizumab (cases where the individual experiences contraindications, suboptimal response, or intolerant to their current treatment for NMOSD).
-use of ravulizumab in individuals diagnosed with NMOSD who are treatment naïve (e.g. first line)

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

Same as #2. CDEC noted that there is "*no evidence to define order of use between rituximab, inebilizumab, satralizumab, eculizumab, or ravulizumab, nor there is evidence for switching from one treatment to another.* " It is not clear if the patient input related to personal/shared decision-making (with a clinician) about administration, benefit vs risk, lifestyle, etc. was considered.

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

The reimbursement conditions have been clearly stated.
In closing, Canadian drug programs must offer the full range of Health Canada-authorized medicines for NMOSD. This includes different classes of medications and administrations as the clinical response to each of these drugs will vary greatly from person to person based on their unique patient journey.

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

CADTH

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	*Jennifer McDonell*
Position	*Director, MS Information and Resources*
Date	*01-03-2024*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

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

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

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	
Brand name (generic)	Ravulizumab
Indication(s)	Anti-AQP-4 Ab-positive NMOSD
Organization	The Sumaira Foundation
Contact information[a]	Name: Sumaira Ahmed

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

We are pleased to see that CADTH is recommending that ravulizumab be reimbursed for the treatment of adult patients with Anti-AQP-4 Ab-positive NMOSD. We do however remain concerned that some of the conditions CADTH has laid out in Table 1 will create additional and continuing barriers to therapy access if not revised.

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 our input was considered and reflected in general in CADTH's draft reimbursement recommendations. However, there are some important points we would like CADTH to take note of and factor into your final recommendation.

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

Table 1 – condition #1: this condition is based on the CHAMPION-NMOSD trial design, yet in TSF's experience, many patients need to change therapies for other reasons, including side effects/intolerability or other signs of disease progression in the judgment of their doctors (e.g., MRI lesion progression). This condition will force patients to "fail" their current therapy by going through another relapse, which can have serious and permanent debilitating consequences. TSF believes the decision to switch therapies should be left to the patients and their doctors.

Table 1 – conditions #2 and 5: NMOSD is a rare but often devastating disease, with no approved on-label therapies until quite recently. Therefore, clinical trial designs are necessarily based on smaller patient numbers with stricter inclusion criteria to ensure statistically valid outcomes. Patients with EDSS scores above 7 still have NMOSD and still need therapies that work, particularly if they continue to have relapses, so just because trials excluded patients with a higher EDSS score does not mean these patients would not benefit from the therapy. We believe the goal should be to prevent all future relapses in all anti-AQP-4 Ab-positive NMOSD patients, regardless of their disability level. Likewise, therapy should not be automatically discontinued for patients even if they reach an EDSS score of 8. This serious decision should be left up to the patient and their doctors, as there are few alternative therapies available.

Table 1 – condition #9: The logic behind CADTH's estimate of $2.4 mn per QALY gained vs. satralizumab is unclear to us and feels high on its face, without a more detailed explanation as to how that number was reached. In addition, CADTH's "Cost and Cost-Effectiveness" table lists ISTs as comparators, yet ISTs are neither indicated for nor proven to be effective therapies for NMOSD. Many of these ISTs, including systemic and oral steroids, have serious and sometimes intolerable side effects, and many NMOSD patients have failed on these off-label therapies, with often permanent vision loss, paralysis or even death. More generally, CADTH cites the need to achieve an ICER of $50,000 per QALY. Extensive research on drug development costs, well-documented in the peer-reviewed literature, make that target QALY ICER unrealistic if CADTH expects therapies to be researched & developed for patients living with rare diseases such as NMOSD. This is especially true for rare diseases where no other existing on-label therapies proven to be effective meet the arbitrary ICER threshold. Furthermore, many other countries are providing reimbursement for the recently approved NMOSD therapies, including relevant comparator country markets in Europe, the USA and elsewhere. TSF encourages all stakeholders in all countries to engage in productive, good-faith, common-sense dialogue regarding reimbursement prices & conditions so that these proven therapies can be made accessible to the patients who clearly need them and would greatly benefit from them.

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

The implementation mechanisms for Table 1 conditions #2, #3, #4, and #5 are unclear, and TSF is concerned that, poorly designed, these conditions could abruptly force patients off therapy or throw them into an administrative limbo while they work through trying to continue on a therapy they and their doctors believe is best for them.

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

Please see our comments regarding "Table 1 – condition #9" above.

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

Appendix 1. Conflict of Interest Declarations for Patient Groups

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A. Patient Group Information	
Name	Sumaira Ahmed
Position	Founder, Executive Director & NMOSD patient
Date	25-02-2024
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

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

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0785
Brand name (generic)	ULTOMIRIS (ravulizumab)
Indication(s)	For the treatment of adult patients with anti-aquaporin 4 (AQP4) antibody-positive neuromyelitis optica spectrum disorder (NMOSD)
Organization	Alexion Pharma GmbH
Contact information[a]	Name: [redacted]

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

Alexion Pharma GmbH (Alexion) agrees with the committee's recommendation. The committee has recognized the important clinical benefits of ULTOMIRIS and its ability to address unmet needs in patients with NMOSD. Providing access to ULTOMIRIS will help eliminate the devastating attacks afflicting patients with NMOSD which can result in permanent neurological and motor disability, thereby preserving patient independence, function, and quality of life. Alexion appreciates the committee for highlighting that "Based on GRADE assessment of selected outcomes from the CHAMPION-NMOSD trial, it was concluded with high certainty that after a median follow-up of 73.50 weeks, treatment with ravulizumab results in a higher probability of having no attack compared to placebo".

The recommended reimbursement criteria (Table 1) is specific to patients who have had at least 1 NMOSD attack/relapse in the previous 12 months. However, input from clinical experts consulted by CADTH notes that "*All individuals with AQP4+ NMOSD should be considered eligible to receive ravulizumab*" (page 7). Notably, ULTOMIRIS treatment consists of every 8-week infusions after the initial loading period and aligns with patient values for access to treatments with less frequent infusion dosing. Clinical experts emphasized that "*patients with a good response on eculizumab may be switched to ravulizumab for convenience of administration*" (page 9). Therefore, Alexion suggests that the reimbursement criteria should also provide consideration for patients wanting to switch for convenience. Patients currently receiving every-2-week eculizumab infusions could benefit from switching to ULTOMIRIS, despite not having had a NMOSD relapse in the last year, due to the additional convenience and the improved quality of life associated with the reduced dosing frequency of every-8-week ULTOMIRIS infusions.

Alexion agrees with CADTH for highlighting clinician and patient input that current treatments (eculizumab and satralizumab) are not accessible. Alexion is committed to working with the pan-Canadian Pharmaceutical Alliance (pCPA) and provincial jurisdictions to ensure that patients with NMOSD ~~to ensure~~ have appropriate and rapid access to ULTOMIRIS and experience its considerable clinical benefits.

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	☐

Alexion agrees with the committee that the results of the CHAMPION-NMOSD trial offer high certainty that ULTOMIRIS can drastically reduce the risk of future NMOSD relapses. Alexion appreciates the committee for recognizing that patients should be eligible for ULTOMIRIS after the

initial diagnostic attack, without having to trial ineffective and poorly tolerated off-label treatments such as glucocorticoids, azathioprine, mycophenolate mofetil, and rituximab.		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
Alexion believes that the reasons for the recommendation are clearly described in the recommendation, which cites the strong clinical data from the CHAMPION-NMOSD trial supporting the use of ULTOMIRIS in the treatment of patients with NMOSD and the ability for ULTOMIRIS to address important unmet patient needs.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
CADTH clearly outlined the issues raised by the provincial drug programs and described clinical expert responses to address implementation concerns. In addition, Alexion agrees with CADTH for highlighting clinical expert input around practical timeframe for EDSS assessment (every 12 months).		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
Overall, the reimbursement conditions and corresponding rationale are clearly described.		

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