CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

RAVULIZUMAB (Ultomiris)

Alexion Pharma GmbH

Indication: For the treatment of adult patients with anti-acetylcholine receptor (AChR) antibody-positive generalized Myasthenia Gravis (gMG).

April 27, 2023

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0765-000
Brand name (generic)	ravulizumab
Indication(s)	AChR antibody-positive generalized Myasthenia Gravis
Organization	Muscular Dystrophy Canada
Contact information[a]	Homira Osman, Vice-President Research & Public Policy

Stakeholder agreement with the draft recommendation

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

We do not agree with CDEC's recommendation. We are surprised by the draft recommendation, particularly as CDEC does not adequately acknowledge the significant unmet needs of patients with generalized myasthenia gravis (gMG) who do not respond to conventional treatments, or who have become resistant to them but also those who remain symptomatic despite existing treatments.

As we heard through our interviews, surveys and the Canadian MG Patient Journey Mapping project, important limitations exist for standard of care therapies due to lack of sustained and consistent control of MG, side effects, quality of life impacts, and unavailability – all which contribute to significant clinical, economic and humanistic burden.

Through our recent Canadian MG Journey Mapping project, we know there are many Canadians whose symptoms persist despite treatment with adequate corticosteroid doses, other ISTs, and/or chronic IVIg, PE, or PP, or whom the doses or frequencies of these therapies cannot be reduced. We also know patients with gMG are often facing treatment decisions and are shifted between treatments or on combination of treatments with undesirable side effects. When consulting with patients on this recommendation, one finding was clear*: physicians should not wait for a patient to "fail" to give them this therapy.* Patients are optimistic that the committee will acknowledge the extended duration required for the positive effects of ISTs like azathioprine, mycophenylate, tacrolimus, and cyclophosphamide to materialize. Consequently, patients may face the negative side effects associated with high doses of corticosteroids needed to obtain a desirable clinical outcome or may remain undertreated, putting them at risk of a MG crisis if corticosteroids are tapered prematurely.

While the committee acknowledges the lack of effective therapies for patients with refractory MG – *"There is an unmet need for effective therapy for patients with refractory gMG"*, it is important to also recognize the significant unmet need for patients with active MG who are not considered refractory but still experience a poor quality of life due to limited or ineffective treatment options. Steroids, steroid-sparing agents, and rituximab, which are commonly used to treat MG, all have significant drawbacks, including delayed onset of action, significant toxicity, and potential for serious side effects such as infections. Therefore, it is crucial to take into account the full range of patient needs when considering treatment options for MG.

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	☒

No, the CADTH Reimbursement Recommendation seems to have not factored in the rich, poignant, valued lived experience input of patients affected by Myasthenia Gravis. In fact, it appears the current set of recommendations is in contrast with the patient input provided and does not align with the learnings of our "Myasthenia Gravis Patient Journey Mapping" project – where an unmet need with treatments was reported. While the patient input was accurately summarized "*Respondents identified an unmet need for new treatments that can decrease the intensity of MG exacerbations, maintain independence, and prevent hospitalization. Patients also desired*

treatments with minimal side effects and convenient administration (e.g., once daily oral administration, easy to swallow, fast onset, long duration of action, low cost), however, indicated they would be willing to accept the side effects of new therapies that better control the consequences of MG", it appears that the committee may not have fully appreciated the importance of ravalizumab in managing patients with MG which include:

- *Extended dosing interval:* Ravulizumab has a longer dosing interval of every 8 weeks compared to other treatments, such as intravenous immunoglobulin (IVIg) or plasma exchange, which need to be administered more frequently. This can reduce the burden of treatment (as well as costs) and improve patient adherence. In fact, one young woman with a young family in BC reported that the psychosocial and financial burden of taking time away from work (i.e., loss of productivity), family (e.g., arranging childcare for IVIg treatments every 4 weeks) is challenging and any treatment that has a longer dosing interval is more preferred.
- *Improved symptoms:* In clinical trials, ravulizumab has been shown to improve the symptoms of myasthenia gravis, including muscle weakness and fatigue. Just like with the patient input submission, fatigue was the most frequently reported bothersome aspect of MG in the MG Canadian Patient Journey Mapping project. Fatigue is particularly bothersome to persons with MG because it can significantly impact their ability to carry out daily activities and lead a normal life. The fatigue in MG is not the same as the normal tiredness people experience after physical exertion or mental stress. Simple tasks such as holding a book or brushing teeth can become difficult and exhausting. One woman spoke about blow drying her hair in the morning requires 2 hours of rest afterwards. As a result of fatigue, persons with MG may have to rely on others for help with routine tasks (informal caregiving), become socially isolated (loss of participation at home, workplace or community; risk for depression and anxiety), and do not work (loss of productivity). Furthermore, fatigue in MG can also affect other aspects of health, such as sleep, mood, and cognitive function. Poor sleep quality due to breathing difficulties or discomfort can exacerbate fatigue, while depression and anxiety are common among people with chronic illnesses like MG. Cognitive impairment, such as difficulties with attention, memory, and processing speed, can also occur in some people with MG and can further contribute to fatigue. Therefore, managing fatigue is an important part of treating MG and should be considered an important outcome/benefit of ravulizumab.

We would like to clarify patients' desire for oral treatment. While yes of course, oral treatments are preferred because they are easy to swallow/take, this preference does not outweigh/negate the potential benefits that can be offered by ravulizumab. From a trade-offs perspective, the benefits of ravulizumab are more preferred than the desire for at-home treatment. An ideal therapy for myasthenia gravis of course would be an orally administered, safe, durable treatment with a quick onset of action. However, it is understood by patients that such a therapy may not be available for several years. In the meantime, ravalizumab represents a major step forward in MG treatment, offering a faster onset of action and a more convenient administration schedule compared to current therapies like eculizumab, IVIg, and plasmapheresis. For patients with MG, ravalizumab is considered one of the most person and family-centric options available.

Ravulizumab provides a new treatment option for patients with myasthenia gravis that has demonstrated efficacy, safety, and improved dosing convenience compared to other treatment options. We are urging the committee to reconsider the rejection of this new therapy for patients. We believe that there are appropriate safeguards in place, including inclusion and exclusion criteria, monitoring, outcomes, and stopping rules, which would allow neuromuscular specialists to use ravalizumab responsibly. It is important for the CDEC committee to carefully consider this input and re-evaluate their decision regarding the use of ravalizumab in managing MG.

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	☐
Not well-discussed as the recommendation was negative.		

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
Not applicable as reimbursement was not recommended.		

[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	*Homira Osman*
Position	*Vice-President, Research and Public Policy*
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 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	SR0765-000
Brand name (generic)	Ravulizumab
Indication(s)	Myasthenia Gravis
Organization	NMD4C Neuromuscular Clinician Group
Contact information[a]	Name: Dr. Hans Katzberg

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

The NMD4C Neuromuscular Clinician Group does not agree with the committee's recommendation that ravulizumab not be reimbursed for treatment of AChR antibody positive myasthenia gravis. The following are point by point comments by the physician group addressing the disagreement:

- **Page 3, Rationale for recommendation:** The committee states that the CHAMPION study did not provide evidence on efficacy and harm of ravulizumab in comparison to conventional immunosuppressive therapies. It is notable that high level comparison data is also not available for other MG therapies. As this kind of analysis is not available in the field of MG therapeutics, this paucity of data should not serve as one of the primary reasons to withhold therapy in this rare and serious disease. This is particularly important for new, effective, safe and convenient therapies designed to target a primary disease driver (complement) in MG. Conversely, ravulizumab did show additional benefit in patients who were on conventional immunosuppressive therapies.

- **Page 3, Rationale for recommendation:** The committee recognizes the unmet need for effective therapies for patients with refractory MG but fails to recognize the similarly important unmet need for patients with active MG who may not fulfil the refractory definition but who cannot achieve a satisfactory quality of life with existing therapies as these are often ineffective, limited, delayed or have significant risk profiles and significant toxicities. This is particularly true for steroids, which have consistent and prominent short and long term toxicity, steroid-sparing agents with delayed onset of action that can take years to take effect and rituximab, which has sustained and irreversible immunosuppression with potential for life threatening infections.

- **Page 3, Rationale for recommendation:** The committee states that patient feedback has identified the hope that new and effective treatments have features, which include convenient administration, ideally oral, durable, safe and with rapid onset. This is indeed a therapy which would be deemed as "ideal", but may not be available for MG for years to come. In the interim, ravulizumab represents an agent with a rapid onset of action, impressive safety profile and administration schedule which is a major advance from current therapies, including eculizumab, IVIG and plasmapheresis and one of the best options in regards to patient-centred therapy in MG.

- **Page 3, Rationale for recommendation and Pages 10/11, Indirect Comparisons and Comparative Observational Evidence:** The committee states that the impact of ravulizumab on hospitalizations and comparable comparison to eculizumab is not supported by evidence.

It should be emphasized that this data does not reflect the primary supportive evidence for use of ravulizumab in MG and that this level of evidence is often not possible to generate due to the methodological issues highlighted by the committee, or only available after years of population level evidence including treatments that are available.

- **Page 4, Discussion points:** The committee highlights that maximal response to IST are typically delayed by 2-6 months, however, this only applies to corticosteroids. Steroid-sparing IST's such as azathioprine, mycophyenolate, tacrolimus, cyclophosphamide and Rituximab can often take considerably longer than this (in many cases one or more years) to take effect. During this period, patients remain vulnerable to the adverse effects expected on high doses of corticosteroids required to achieve a desired clinical response or undertreated and at risk for MG crisis if corticosteroids are tapered. Furthermore,a sizeable number of patients are unable to tolerate some of these ISTs. Of note, acetylcholine receptor inhibitors are insufficient to maintain clinical stability in generalized AChRAb positive MG.

- **Page 4, Discussion points and Page 10, Pivotal Studies critical appraisal:** The committee highlights that the fact that steroids or other IST's were not allowed to be tapered during the trial in a significant manner did not reflect clinical practice. As this is a standard in clinical trials where steroid sparing effects is not the primary outcome, this should not negate the efficacy of the treatment being evaluated. This topic is likely to be the focus of ongoing and follow-up real-world studies using ravulizumab in MG.

- **Page 4, Discussion points:** The committee states that the CHAMPION study did not evaluate exclusively refractory patients and that currently available standard therapies are generally effective in most patients with MG. Although these points are correct, as stated above that there is an unmet need in non-refractory, severe MG who either experience a considerable delay or inadequate MG-post intervention status despite using 2 IST's. There is also a significant advantage to refractory patients eligible for complement therapy who would benefit from the considerably less frequent infusions of ravulizumab compared to eculizumab.

- **Page 5, Background:** The committee recognizes that chronic IVIG or plasmapheresis is often used as maintenance or bridging therapy in patients with MG who are not adequately managed with conventional oral immunotherapy. It should be noted that these therapies are limited due to a) venous access issues which may be difficult to overcome b) potentially serious cardiovascular and systemic adverse effects or contraindications to these therapies c) waning efficacy in spite of an initial response to IVIG or PLEX d) considerable infusion/transfusion requirements which make these efforts unsustainable e) lack of supply of product (IVIG or SCIG) that threatens to interrupt therapy abruptly to the detriment of patients. Finally, PLEX is available in very few large centers in each province and IVIg can only be infused in hospital infusion rooms across the country that entails considerable delay instituting this therapy.

- **Page 10, Pivotal Studies critical appraisal:** The committee states that based on the CHAMPION study, it is not possible to ascertain the outcome of prior therapies received in the study population. They further reference comments by the clinical experts that earlier lines of therapy for non-refractory MG generally have high response rates and that these patients are more likely to respond to any therapy compared to those later in the treatment course. While this may be true for patients with mild disease, there remains a significant number of patients with moderate-severe MG who are not yet refractory who continue to fail treatment trials or

have partial responses with medications which are more toxic and with slower onset of action. The majority of patients entering the CHAMPION study were not treatment naive and likely included this challenging group of patients managed by the neuromuscular experts who are signatories on this feedback letter. As such we are strongly advocating to the committee to not limit the tools available to us to carefully select these patients who are at high risk of becoming refractory and enter a refractory state which can have major mortality and morbidity implications as well as ultimately being unable to reverse despite all efforts.

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	☒

Although the committee summarized the input from the clinician experts and our clinician input group, it is our impression that the committee underestimated the importance and key role ravulizumab would play in the management of patients with MG. As such, we cannot state that the committee appropriately considered the stakeholder input, which was provided and urge the committee to reconsider the blanket rejection of this new therapy for patients. As stated by both stakeholder groups and in the considerations in section 1 above, there are careful safeguards including inclusion and exclusion criteria, monitoring, outcomes and stopping rules which would allow ravulizumab to be utilized responsibly by clinicians. This is further supported by what our group considers to be appropriate use of eculizumab years after its approval in Canada.

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	☒

The committee obtained input from drug programs that participate in the CADTH reimbursement review process to identify key factors that could potentially impact. This included issues relating to relevant comparators, care provisions issues, system and economic issues as well as consideration for initiation, continuation, renewal, and discontinuation and prescribing of therapy. In spite of this consultation, there was no additional details provided relating to these implementation issues, likely as the recommendation from the committee was not to reimburse.

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

Not applicable as reimbursement was not recommended.

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

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0765-000
Brand name (generic)	Ultomiris (ravulizumab)
Indication(s)	AChR antibody-positive generalized Myasthenia Gravis
Organization	Canadian Organization for Rare Disorders (CORD)
Contact information[a]	Name: Durhane Wong-Rieger

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.

The Canadian Organization for Rare Disorders (CORD) is responding to the draft recommendation on behalf of patients seeking assistance to express their shock and dismay in learning that Ultomiris had not been recommended by the CDEC committee for the treatment of generalized Myasthenia Gravis (gMG). We concur with their sentiments, especially in the context of previous positive CADTH recommendations for Soliris for gMG and the positive CADTH recommendations for Ultomiris for PHN and aHUS. It is not clear why CDEC should have chosen to treat Ultomiris for gMG differently, that it should have been an outlier. The committee chose to focus on aspects of the clinical trial for ravulizumab that were not raised for the other trials for Soliris for PNH, aHUS, and gMG as well as in recommendations for Ultomiris for PNH and aHUS. The antibodies and the mechanism of action for Soliris and Ultomiris are the same; their efficacy against placebo are virtually the same, and the adverse effects profile similar. The key difference is that Ultomiris is long-acting so requires less frequent dosing.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provid ed to CADTH?	Yes	☐
	No	☒

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

The committee did not consider the stakeholder input appropriately. In the one patient submission, the patients hopes and expectations for an "ideal" treatment included attributes that were idealistic, including less intense symptoms, fewer hospitalizations, ease of use (oral therapy), and longer duration. Given that Ultomiris is not considered a more efficacious treatment that Soliris (non-inferior) but longer lasting, the patients' wishes should NOT be used as a justification for concluding that Ultomiris did not meet patient expectations or would be preferable to Soliris.

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.

The committee based their negative recommendation, in part, on the fact that there had been no explicit trial comparisons with standard of care, namely immunosuppressive therapy (IST) and steroids and also that there was no differentiation between refractory patients and those who were not in the trials. None of these issues were cited in the Soliris trials or the CTs for Ultomiris for other indications. Perhaps most egregious among the rationale provided for not recommending was the reason that Ultomiris did not meet patient expectations, that is, all of them. The drug DOES require less frequent injections, which is of considerable impact on quality of life, despite the claim that it does.

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.

The committee recognizes that screening and testing are not barriers to use. Moreover, there should be no difference in treating and monitoring patients with Ultomiris compared to Soliris. The recommendation ignores the less onerous treatment regime for Ultomiris compared to Soliris.

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.

Given the negative recommendation and the requests for more clinical trial data, it will be very easy for the public plans to deny and difficult to pursue through alternate pathways. It is also highly inappropriate to conduct a CE calculation with drugs and diseases like this.

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

Appendix 1. Conflict of Interest Declarations for Patient Groups

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- 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	*Canadian Organization for Rare Disorders*
Position	*President & CEO*
Date	*27/04/2023*
☒	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**
Alexion	☐	☐	☒	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0765
Name of the drug and Indication(s)	Ravulizumab (Ultomiris) for Myasthenia Gravis (gMG)
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.

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.