CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

inebilizumab (Uplizna)

(Neuromyelitis optica spectrum disorders (NMOSD))

Indication: Indicated as monotherapy for the treatment of adult patients with neuromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive.

March 1, 2024

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0793-000
Brand name (generic)	UPLIZNA® (inebilizumab)
Indication(s)	Neuromyelitis optica spectrum disorder (NMOSD)
Organization	Canadian Network of Multiple Sclerosis (MS) Clinics (CNMSC)
Contact information[a]	Name: Dr. Dalia Rotstein

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
Overall, CNMSC finds the draft recommendation for inebilizumab in NMOSD reasonable and practical. Some suggestions for clarification, etc. have been identified below.		

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	☐
Overall, the recommendation appears to have considered the input provided by CNMSC. See item 3 below for issues previously raised by CNMSC that have not been addressed.		

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

The CNMSC feels that the recommendation needs to be clarified in the following areas:

a) Comparators

- It is not clear in the recommendation what the committee considers to be the "lowest cost comparator." In the Discussion Points, the document mentions that the clinical experts did not consider rituximab to be a comparator to inebilizumab, satralizumab, or eculizumab because of its off-label use. However, CDEC's position is not clarified.

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

The CNMSC feels that the recommendation needs to be clarified in the following areas:

a) Role in rituximab failures

- It is implied (but not clear, as noted above) that the comparator is rituximab.
- The recommendation does not address the role of inebulizumab in patients who fail on rituximab, which is a highly relevant clinical question.
- This gap in the recommendation overlooks the input provided by CNMSC and the clinician consultants; specifically, that there are some potential mechanistic advantages of

inebulizumab, as an anti-CD19 therapy that directly targets plasmablasts, over the existing options that would be particularly relevant for patients with severe and/or refractory disease.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
CNMSC understands that a price reduction is necessary to optimize the value of this product for public/government drug plans.		

[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		
1. Did you receive help from outside your clinician group to complete this submission?	No	☐
	Yes	☒
A pharmaceutical policy consultant (Dr. Judith Glennie, Aurora, Ontario) supported the development of the first draft of this submission and revisions from the reviewing physicians. All revisions were reviewed and approved by the lead author of the submission.		
2. 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		
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: • Dalia L. Rotstein • Mark Freedman • Jiwon Oh • Jodie Burton • Natalie Perks • Penny Smyth • Fraser Clift • Guilia Fadda • Francis Brunet		

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)*

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0793
Name of the drug and Indication(s)	Inebilizumab (Uplizna) as monotherapy for the treatment of adult patients with neuromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive.
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	SR0793-000
Brand name (generic)	UPLIZNA® (inebilizumab)
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	☐

MS Canada feels the draft recommendation for inebilizumab in NMOSD is appropriate. However, it is not clear if inebilizumab is a first-line option for individuals who are treatment naïve.

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. We will use this opportunity to reiterate the importance of access to all Health Canada-approved treatments for NMOSD, which should be employed as first-line treatment options instead of off-label options that lack Phase 3 trial data in NMOSD.

Clarity of the draft recommendation

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

The recommendation is clear except for #9 "Pricing".

"Inebilizumab should be negotiated so that it does not exceed the drug program cost of treatment with the least costly comparator reimbursed for the treatment of adults with NMOSD who are AQP4-IgG seropositive."

It is not clear what the comparator is, and therefore what inebilizumab will be negotiated against. Rituximab was used in the absence of high-efficacy agents indicated for NMOSD. With multiple Health Canada-approved treatments indicated for NMOSD now available, rituximab (especially biosimilar rituximab) should not be used as a price comparator. MS Canada feels the price should be negotiated fairly against other contemporary Health Canada-approved comparators for NMOSD.

Inebilizumab is the only Health Canada-approved B-cell therapy for NMOSD and should be the first-line option rather than rituximab when a B-cell therapy is identified as the most suitable therapy. Otherwise, individuals are being treated based on cost-savings versus the most optimal treatment for their disease course.

	Yes	☐

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	No	☒
-MS Canada advocates for access to all Health Canada-approved medications for NMOSD as it is critical for individuals to switch therapies if they have a suboptimal response or are intolerant to the medication they are currently taking. -It is not clear from the recommendations what the process would be to switch from rituximab, or other NMOSD treatments to inebilizumab.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes No	☒ ☐
The majority of conditions are clear. Those lacking clarity include first-line listing and the comparator for pricing negotiations. 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	SR0793-000
Brand name (generic)	UPLIZNA® (inebilizumab for injection)
Indication(s)	Inebilizumab is indicated as monotherapy for the treatment of adult patients with neuromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive.
Organization	Horizon Therapeutics Canada (Horizon)
Contact information[a]	[redacted]

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

Horizon agrees with the committee's assessment that, "*among AQP4 seropositive patients, treatment with inebilizumab likely results in a clinically meaningful increase in time to first relapse and a reduction in the proportion of patients with worsening in EDSS compared to treatment with placebo after 197 days of treatment*". Additionally, Horizon agrees that "*inebilizumab met some important patient needs by reducing the risk of future attacks, as well as slow[ing] disease progression*". Horizon also believes that the initiation criteria for inebilizumab (i.e., adult patients with NMOSD who are AQ4P-seropostive and have had ≥1 attack in the prior 12 months or ≥ 2 attacks in the prior 2 years) reflects the appropriate place in therapy and is aligned with the inclusion criteria of the pivotal trial and patient needs.

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	☐

Horizon agrees that the recommendation reflects patient and clinician group input, as "*patients identified a need for accessible therapies to reduce the frequency and severity of NMOSD attacks and the associated progression of disability, loss of HRQoL, and loss of independence.*" The clinical experts consulted by CADTH agreed that "*the greatest unmet need in the treatment of NMOSD is for therapies that more effectively prevent relapses without intolerable side effects".*

Horizon would like to highlight the clinical expert feedback on immunosuppressive therapies, which further emphasizes the unmet need for effective and tolerable, on-label therapies in the treatment of NMOSD: *"The clinical experts also noted that patients should not be required to trial immunosuppressive therapies before access to inebilizumab. The listed immunosuppressive treatments (rituximab, azathioprine, or mycophenolate mofetil) are used off-label, are not considered particularly effective in this population based on clinical practice, are associated with significant side-effects, and have very little data available in patients with NMOSD. Additionally, broad immunosuppressant therapies are considered to be symptomatic treatments only, not disease-*

modifying therapies, in contrast to the targeted monoclonal antibodies such as inebilizumab which target underlying pathophysiology. As any attack may have permanently disabling consequences, it is clinically inappropriate to require patients with this disease to trial ineffective therapies that have little evidence."

Clarity of the draft recommendation

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

Horizon believes the reasons for the recommendation are clearly stated.

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

Horizon believes the implementation issues have clearly been articulated and adequately addressed in the recommendation.

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

Horizon believes that the Pricing condition should more clearly specify that inebilizumab should be negotiated so that it does not exceed the drug program cost of treatment with the least costly *Health Canada-approved comparator.*

The Discussion Points (page 6) of the draft recommendation revealed that, "*regarding the pricing condition, CDEC discussed that rituximab was the lowest cost comparator included in the review and noted that it is used off label, without an indication for the treatment of NMOSD. CDEC recognized that clinical expert input did not consider rituximab to be a comparator to inebilizumab, satralizumab, or eculizumab in this context*". Furthermore, in the response to Drug Programs (page 11, 12), clinical experts noted that "*rituximab has very limited clinical evidence in the treatment of NMOSD, while there is phase 3 data supporting the efficacy of inebilizumab for this condition. Given the severity of the disease, even 1 attack may be permanently disabling, ergo it may be considered inappropriate to use rituximab in place of inebilizumab*." In addition, the clinical experts noted that "*although rituximab and inebilizumab both suppress B-cells, there is some evidence that patients with F allele polymorphism at amino acid 158 of the FCGR3A gene (F158) may have an incomplete response to rituximab (anti-CD20) but not to inebilizumab (anti-CD19)*."

Horizon agrees with the clinical expert input that it would be inappropriate to consider rituximab as a comparator to inebilizumab.

Off-label rituximab has historically been used in Canadian clinical practice when there were no reimbursed, evidence-based alternatives to treat patients. However, an effective Health-Canada approved targeted therapy (i.e., satralizumab) is now reimbursed by provincial drug programs in Canada. Therefore, Horizon respectfully requests that an editorial revision is made so that the pricing condition in Table 1 is modified to state: *"Inebilizumab should be negotiated so that it does not exceed the drug program cost of treatment with* ***satralizumab***". In the CADTH draft recommendation for ULTOMIRIS (ravulizumab) for the treatment of AQP4 antibody-positive NMOSD, CADTH did not conduct a reanalysis of the pharmacoeconomic evaluation and recommended a price reduction based on the ICER in the sponsor's analysis of ravulizumab versus satralizumab. Given that satralizumab is the only reimbursed therapy with an approved indication for the treatment of adults with NMOSD who are AQP4-IgG seropositive and the recommended price reduction for ravulizumab was anchored to satralizumab, Horizon believes the requested modification to the pricing condition for inebilizumab is appropriate and equitable.

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

Abbreviations: AQP4 = anti-aquaporin-4; CADTH = Canadian Agency for Drugs and Technologies in Health; CDEC = Canadian Drug Expert Committee; EDSS = Expanded Disability Status Scale; HRQoL = health-related quality of life; IgG = immunoglobulin G; NMOSD = neuromyelitis optica spectrum disorders.