



## CADTH Reimbursement Recommendation

# Inebilizumab (Uplizna)

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

**Sponsor:** Horizon Therapeutics Canada

**Final recommendation:** Reimburse with conditions



# Summary

## What Is the CADTH Reimbursement Recommendation for Uplizna?

CADTH recommends that Uplizna be reimbursed by public drug plans for the treatment of neuromyelitis optica spectrum disorder (NMOSD), if certain conditions are met.

### Which Patients Are Eligible for Coverage?

Uplizna should only be covered to treat adult patients who are anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive and who have had at least 1 NMOSD relapse episode (also known as an “attack”) in the 1 year before initiation, or 2 NMOSD relapse episodes in the 2 years before initiation. Patients must have an Expanded Disability Status Scale (EDSS) score of 8 points or less.

### What Are the Conditions for Reimbursement?

Uplizna should only be reimbursed if it is prescribed by neurologists with expertise in treating NMOSD and the cost of Uplizna is reduced to be no greater than the least costly comparator currently reimbursed for the treatment of NMOSD. Uplizna should not be initiated during a NMOSD relapse episode or when used in combination with rituximab, satralizumab, eculizumab, or ravulizumab.

### Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that patients treated with Uplizna had a longer time to first NMOSD relapse and had less worsening in EDSS compared to patients treated with placebo.
- Uplizna may meet important patient needs by reducing the risk of future NMOSD relapses, as well as by slowing disease progression.
- CADTH was not able to estimate the cost-effectiveness of Uplizna against any comparator treatment. The committee determined that there is not enough evidence to justify a greater cost for Uplizna compared with other currently reimbursed treatments for NMOSD.
- Based on public list prices, Uplizna is estimated to cost the public drug plans approximately \$12.5 million over the next 3 years. However, the actual budget impact is uncertain because the size of the eligible population is uncertain.



# Summary

## Additional Information

### What Is NMOSD?

NMOSD is a severe, chronic, and progressive disease of the central nervous system, in which patients experience relapse episodes that cause inflammation in the optic nerve and spinal cord. NMOSD relapses are unpredictable and cause permanent neurologic damage, leading to increasing amounts of irreversible impairment of vision and/or mobility, and sometimes death due to respiratory failure. Over time, patients may experience progressively increasing disability, pain, and loss of independence due to the cumulative effect of repeated relapses. NMOSD is rare and disproportionately affects females. It was estimated that the prevalence ranges from 0.51 to 4.4 per 100,000 people, but there are no Canada-specific estimates.

### Unmet Needs in NMOSD

Patients with NMOSD expressed a need for accessible treatments that are effective in the prevention of NMOSD relapses, as reducing or avoiding relapses is expected to delay the progression of disability and increase patients' ability to maintain independence and health-related quality of life (HRQoL).

### How Much Does Uplizna Cost?

Treatment with Uplizna is expected to cost approximately \$230,607 per patient in the first year and \$153,738 in each subsequent year.

## Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that inebilizumab be reimbursed as monotherapy for the treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive only if the conditions listed in [Table 1](#) are met.

## Rationale for the Recommendation

One double-blind, phase II/III randomized controlled trial (RCT) (the N-MOMentum trial, N = 230) in patients with NMOSD demonstrated that, among patients who are AQP4-IgG seropositive (N = 213), 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 Expanded Disability Status Scale (EDSS) score compared to treatment with placebo after 197 days of treatment. Among patients who are AQP4-IgG seropositive, the hazard ratio (HR) for time to first adjudication committee (AC)-determined NMOSD relapse episode was 0.28 (95% confidence interval [CI], 0.12 to 0.42; P < 0.0001), and at day 197, 87.6% of patients in the inebilizumab group were relapse-free compared to 56.6% in the placebo group, which equated to a 77.3% reduction in the risk of AC-determined NMOSD relapse. The CADTH review of the sponsor's submitted indirect treatment comparisons (ITCs) concluded that inebilizumab did not offer a benefit relative to eculizumab, and that imprecision in the estimated HR prevented a definitive conclusion from being reached in the comparison with satralizumab.

Patients expressed a need to have access to therapy options that can reduce the risk of future relapses, help them maintain their current level of physical ability, and slow disease progression. CDEC concluded that inebilizumab met some important patient needs by reducing the risk of future relapses, as well as by slowing disease progression.

Due to limitations in the pharmacoeconomic model, it was not possible to estimate the incremental cost-effectiveness of inebilizumab in adults with NMOSD who are AQP4-IgG seropositive. CDEC therefore considered the results of a cost-comparison analysis considering drug costs alone. At publicly available list prices for the comparators, inebilizumab was more costly than off-label rituximab and satralizumab, and less costly than eculizumab. Given that no conclusions can be drawn about the comparative effectiveness of inebilizumab relative to the comparator treatments, the total drug cost of inebilizumab should not exceed the total drug cost of the lowest cost comparator that is reimbursed for patients in this setting.

**Table 1: Reimbursement Conditions and Reasons**

Reimbursement condition	Reason	Implementation guidance
<b>Initiation</b>		
1. Adult patients with NMOSD who are AQP4-IgG seropositive and have had $\geq 1$ attack in the prior 12	The N-MOMentum trial showed a benefit of inebilizumab in patients with a documented history of either $\geq 1$ acute NMOSD attack	CDEC noted that "attack" and "relapse" are used interchangeably in NMOSD clinical practice.

Reimbursement condition	Reason	Implementation guidance
months or $\geq 2$ attacks in the prior 2 years.	in the prior year or $\geq 2$ attacks in the prior 2 years that required rescue therapy.	
2. Patients must have an EDSS score of 8 points or less.	Patients enrolled in the N-MOMentum trial were required to have an EDSS score of 7.5 points or less at baseline, or a score of 8 in special circumstances (i.e., if the investigator and medical monitor assessed that the patient was reasonably able to complete the study).	—
3. The maximum duration of initial authorization is 12 months.	Authorization of funding for 12 months provides flexibility to accommodate the practical challenges of assessing clinical response after treatment initiation given the natural history of NMOSD.	—
<b>Renewal</b>		
4. The physician should measure and provide EDSS scores every 12 months after the initial authorization to determine if the continuation of inebilizumab reimbursement should occur.	Annual assessments will help ensure the treatment is used for those benefiting from the therapy and would reduce the risk of unnecessary treatment. In addition, annual assessment is reasonable for stable patients based on input from the clinical experts.	—
<b>Discontinuation</b>		
5. Reimbursement of inebilizumab treatment should be discontinued if the patient's EDSS score is greater than 8 points.	The N-MOMentum study did not apply defined study treatment discontinuation criteria.  Given the natural history of NMOSD, CDEC concluded that preventive treatment for relapse is likely of limited clinical benefit when patients are severely disabled, corresponding to an EDSS score greater than 8 points.	—
<b>Prescribing</b>		
6. The prescribing of inebilizumab for the treatment of NMOSD should be restricted to neurologists with expertise in treating NMOSD.	Accurate diagnosis of NMOSD is important to ensure that inebilizumab is prescribed to the appropriate patients. In addition, several treatment options must be considered when selecting the most appropriate therapy for patients who have NMOSD.	—
7. Inebilizumab should not be initiated during a NMOSD relapse episode.	Inebilizumab acts to prevent, not treat, relapses of NMOSD. There is no evidence to support starting treatment with inebilizumab during a NMOSD relapse episode.	—

Reimbursement condition	Reason	Implementation guidance
8. Inebilizumab should not be reimbursed when used in combination with rituximab, satralizumab, eculizumab, or ravulizumab.	There is no evidence to support the use of inebilizumab in combination with rituximab, satralizumab, eculizumab, or ravulizumab.	—
<b>Pricing</b>		
9. 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.	There is insufficient evidence to justify a price cost premium for inebilizumab over the least expensive comparator reimbursed for adults with NMOSD who are AQP4-IgG seropositive. This is due to the conclusion that inebilizumab is not superior to eculizumab and an inability to draw conclusions from indirect comparisons with satralizumab and off-label rituximab.	—
<b>Feasibility of adoption</b>		
10. The feasibility of adoption of inebilizumab must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate(s).	—

AQP4-IgG = immunoglobulin G autoantibodies for aquaporin 4; CDEC = Canadian Drug Expert Committee; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorder.

## Discussion Points

- Patient group input identified a need for accessible therapies to reduce the frequency and severity of NMOSD relapses and the associated progression of disability, loss of health-related quality of life (HRQoL), and loss of independence. Inebilizumab could address some of these unmet needs. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of selected outcomes from the N-MOmentum trial concluded with moderate certainty that treatment with inebilizumab likely results in a higher probability of having no relapse at 197 days compared to placebo. Moderate certainty of evidence showed that inebilizumab likely results in a reduction in the proportion of patients who have worsening from baseline in disability, as measured by EDSS, compared to placebo at 197 days. Other secondary or exploratory outcomes assessed in the N-MOmentum trial were less conclusive and did not show a clearly meaningful benefit of inebilizumab over placebo, and GRADE assessment of evidence was of low to moderate certainty. These outcomes included change in low-contrast visual acuity score, NMOSD-related inpatient hospitalizations, HRQoL, and pain. The reasons for this incongruence are uncertain but it may be that the duration of the randomized study was insufficient to detect clinically meaningful differences in these outcomes.

- Patients were excluded if they had used rituximab 6 months before screening, and they were not permitted to use rituximab during the N-MOmentum study. The clinical experts noted to CDEC that rituximab is potentially used as a first-line therapy for the prevention of relapses in NMOSD. Therefore, the generalizability of results of the N-MOmentum trial among patients with a recent history of use of rituximab is uncertain.
- The clinical experts noted to CDEC that discontinuation based on disability score should be a medical decision rather than a coverage decision due to the complexities of measuring disability in NMOSD and the lack of a validated scale in this population. EDSS is not validated in NMOSD and has limitations for assessing disability outside of ambulatory disability in this population (e.g., visual acuity, other forms of paralysis). CDEC heard that although EDSS is not validated in NMOSD, it is used in clinical practice and is presently the best available tool to assess response.
- ITCs included matching-adjusted indirect comparisons (MAICs) comparing inebilizumab to satralizumab and eculizumab, and individual patient data (IPD) analyses comparing inebilizumab to rituximab. Results were inconclusive for the comparison to satralizumab. The ITCs suggest that risk of NMOSD relapse is higher with inebilizumab treatment than eculizumab treatment, but the magnitude of benefit is uncertain due to wide 95% CIs, imprecision, and unresolved between-trial heterogeneity. The comparison to rituximab could not be interpreted due to limitations in the analysis inherent to the data available as well as sparsely reported methodology and results and inappropriate methodological decisions. There are no direct or indirect data available for the efficacy and safety of inebilizumab compared to azathioprine, mycophenolate mofetil, or ravulizumab.
- CDEC discussed that there is no evidence to define order of use between rituximab, inebilizumab, satralizumab, eculizumab, or ravulizumab, nor is there evidence for switching from 1 treatment to another, and the place in therapy of inebilizumab is uncertain. In addition, there was no evidence presented to conclude the most cost-effective sequence of treatments.
- 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. Drug plans may or may not consider rituximab a relevant comparator in their negotiations. In the case where the drug plans do not consider rituximab to be a comparator for the purpose of price negotiations, the lowest cost comparator should be based on the lowest negotiated treatment cost among the remaining treatments within this analysis (i.e., satralizumab, eculizumab).

## Background

NMOSD is a rare, chronic disorder of the central nervous system that is characterized by acute relapses that cause inflammation in the optic nerve (optic neuritis) and spinal cord (myelitis). A defining feature of NMOSD is the presence of pathogenic serum autoantibodies against AQP4, which differentiates it from multiple sclerosis (MS). NMOSD relapses are unpredictable, and they can lead to accruing disabilities and often to

permanent impairment. The clinical presentation of an NMOSD relapse typically involves optic neuritis that causes ocular pain and vision loss. Myelitis causes sensory loss, weakness or paralysis in the legs or arms, painful spasms, and bladder and bowel dysfunction. At its worst, severe high cervical myelitis and brainstem lesions can lead to fatal respiratory failure. The consequences of NMOSD extend beyond clinical settings and include physical, functional, and psychological effects that alter every aspect of patients' and caregivers' lives and impact their HRQoL.

NMOSD disproportionately affects females. Systemic reviews based on data from several countries have estimated 0.053 to 0.4 incident cases per 100,000 people and 0.51 to 4.4 prevalent cases per 100,000 people. No Canada-specific estimates were identified in these studies.

Inebilizumab has been approved by Health Canada as a monotherapy for the treatment of adult patients with NMOSD who are AQP4-IgG seropositive. Inebilizumab is a humanized, afucosylated monoclonal antibody that binds to CD19 for the treatment of NMOSD. The recommended dosage for inebilizumab is an initial 300 mg dose via IV infusion, followed 2 weeks later by a second 300 mg dose via IV infusion; subsequent doses (starting 6 months from the first infusion) are administered as single 300 mg doses via IV infusion every 6 months. Inebilizumab should be administered under the supervision of a qualified health care professional.

## Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 randomized controlled clinical study in patients with NMOSD and a single-arm, open-label long-term extension (LTE) of this study
- patient perspectives gathered by 2 patient groups, MS Canada and The Sumaira Foundation (TSF)
- input from public drug plans that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with NMOSD
- input from 1 clinician group, the Canadian Network of Multiple Sclerosis Clinics (CNMSC)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

## Stakeholder Perspectives

### Patient Input

Two patient groups, MS Canada and TSF, responded to CADTH's call for patient input on this topic.

MS Canada gathered information for this submission via an online survey in 2023 that included 13 respondents. TSF gathered information through 2 online surveys and videoconferencing interviews in 2023 with patients and caregivers, and through TSF's experience working in the NMOSD communities. The TSF survey data included 51 patients and 9 caregivers.

The 2 patient groups indicated that NMOSD follows a relapsing-remitting disease course and is initiated with a severe episode and continues with subsequent devastating relapses that affect their vision and lead to mobility issues and chronic pain. The disease has a tremendous impact on all aspects of patients' and caregivers' lives, including a negative effect on their quality of life; independence; employment; and social, family, and school life.

The patient input stated that treatment for NMOSD involved IV steroids and IV immunoglobulin or plasmapheresis or plasma exchange, as well as the use of off-label agents with varying levels of therapeutic benefit (due to worsening symptoms and/or challenging side effects while cycling through different therapies).

According to 2 patient inputs, access is very limited for therapies such as eculizumab, satralizumab, and rituximab, and the administration schedule of eculizumab can be too arduous for some patients. According to patient input, patients need to have access to therapy options that can reduce the risk of future relapses, maintain their current level of physical ability, and slow disease progression.

## Clinician Input

### Input From Clinical Experts Consulted by CADTH

The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of NMOSD.

#### *Unmet Needs*

The clinical experts indicated that treatment of NMOSD includes a series of treatment goals relating to 3 broad areas: prevention of relapses (disease-modifying), treatment of relapses, and treatment of residual symptoms. Although ideal, it is unlikely that any single treatment would cover all 3 areas. Of these 3 areas, preventive treatment was noted to be of special interest because relapses are the major source of disability accumulation for persons with NMOSD. As a result, preventive treatment is expected to result in downstream desirable effects, including better HRQoL, increased ability to maintain independence and employment, and less reliance on caregivers. The clinical experts highlighted that it is important to control progression as early as possible because damage leading to neurologic disability, including paralysis and blindness, may be irreversible after a relapse.

The clinical experts agreed that most patients with NMOSD still have relapses despite their current treatment regimens, and current first-line therapies (e.g., azathioprine and mycophenolate mofetil) are not considered particularly effective in prevention of NMOSD relapses. Additionally, these therapies are also associated with significant adverse effects, especially if used in conjunction with corticosteroids. The greatest unmet need in the treatment of NMOSD is for therapies that more effectively prevent relapses without intolerable side effects.

#### *Place in Therapy*

The clinical experts agreed that the current clinical practice for treatment and relapse prevention in NMOSD is suboptimal and inconsistent, due to the low efficacy of off-label treatments used in the first-line setting

and barriers to treatment access, which varies by province. Newer therapies with indications for NMOSD, such as satralizumab and eculizumab, have especially significant barriers to access for most patients due to inconsistent coverage or lack of public reimbursement, and the onerous dosing schedule of eculizumab. Due to the impact of NMOSD on a person's ability to maintain employment, patients with NMOSD are more likely to lack private insurance.

As the vast majority of patients with NMOSD will relapse, and relapses may lead to permanent disability or death, all people with NMOSD should be on relapse-preventive treatment.

The experts agreed that the impact of relapses on people with NMOSD is devastating, and preventing as many relapses as possible is critical in the prevention of significant disability; thus, inebilizumab should be available as a first-line and later-line treatment for patients diagnosed with NMOSD who are AQP4-IgG seropositive. The experts indicated that inebilizumab would be used as a monotherapy.

### ***Patient Population***

NMOSD is a rare disease. The clinical experts indicated that patients diagnosed with NMOSD who are seropositive for AQP4-IgG should be candidates for treatment with inebilizumab. It is standard of care in Canada to assess patients with NMOSD for AQP4-IgG; the experts noted that there are no major challenges in this regard in Canada, other than some areas potentially experiencing delays in receiving their results. The specificity of AQP4-IgG is very high, so the risk of misdiagnosis is very low.

The patient eligibility criteria in the pivotal N-MOMentum study were considered by the experts to be broadly representative of patients with NMOSD in Canada, with the exception that the study excluded patients with recent steroidal treatment. Although appropriate from the perspective of clinical trial design, in real-world practice there are many comorbidities that may require steroid treatment, and these patients should not necessarily be excluded from treatment with inebilizumab; this decision would be a consideration by the expert clinician managing their particular case. Patients who have received IV immunoglobulin (IVIG) or have concomitant diseases should not necessarily be excluded from receiving inebilizumab in a real-world setting.

Within the population of patients who have NMOSD and are AQP4-IgG seropositive, it is unknown which patients are more likely to benefit from inebilizumab.

It is possible that patients who are seronegative for AQP4-IgG may also benefit from inebilizumab. Fulfillment of seronegative NMOSD criteria would be necessary to establish the diagnosis to allow appropriate access.

### ***Assessing the Response to Treatment***

The experts indicated that a clinically meaningful response to treatment relates to the reduction of the relapse rate and prolonged times to relapse. Although the absence of relapse is indicative of a clinically meaningful response, this may not be realistic, as the number and severity of relapses patients experience differ on an individual level (e.g., some patients may have several relapses per year) and thus a reduction in the number of relapses is still a reasonable goal. The determination of relapses is fairly objective. However, it is not the only factor, and assessment of treatment response is based on a combination of patient reported

symptoms, clinical exam, clinical tools, and patient history. Other important outcome measures include relapse severity and degree of recovery from relapse, as well as accumulation of disability.

The experts noted that there is a lack of formal guidance on how to assess treatment response, but it would be reasonable to assess initial treatment response 3 months after the initial injection, and then every 6 months until stability is achieved, and then every year for persons with stable NMOSD. However, it was noted that within the first 6 months of treatment, the relapse rate may still be higher than when stability is achieved.

MRIs are not routinely conducted for patients with NMOSD outside of initial diagnosis, and so would not be used in assessing the response to treatment.

### ***Discontinuing Treatment***

Discontinuation of treatment should occur if the patient is completely dependent and physically unable to leave bed (EDSS score 9.0 or higher).

Discontinuation of treatment should be considered on a case-by-case basis in the event of a severe relapse (e.g., requiring intubation and support on a ventilator), if the patient is experiencing 2 or more relapses within 2 years, severe or unacceptable adverse events (AEs), or contraindications to therapy.

### ***Prescribing Considerations***

The clinical experts agreed that treatment should be supervised by a neurologist with expertise in this area. Although NMOSD and MS are not the same disease, the populations and medications are similar and persons with NMOSD are often cared for in MS clinics. The clinical experts noted that inebilizumab should be prescribed by neurologists with experience or expertise in related subspecialties, including MS neurology (and/or working as a neurologist in an MS clinic), neuroimmunology, autoimmune neurology, and neuro-ophthalmology. However, patients in remote areas may have issues with access to subspecialists. For patients living in remote areas, local neurologists without subspecialty expertise may work by distance in conjunction with neurologists who are experts in a relevant subspecialty.

Inebilizumab is expected to be used as a monotherapy and is not expected to be combined with other monoclonal antibodies indicated for the treatment of NMOSD. However, there may be situations in which it is combined with classical immunosuppressants. There is a lack of data regarding combination therapies.

### **Clinician Group Input**

One clinician group (the CNMSC, represented by 1 clinician), responded to CADTH's call for clinician group input.

According to the CNMSC, there is a variety of off-label therapies used for the treatment of NMOSD in Canada, including corticosteroids, azathioprine, mycophenolate mofetil, and rituximab. However, breakthrough NMOSD relapses are reported with all of these agents, and government drug program funding varies by province and territory. Recently, 2 monoclonal antibodies, eculizumab and satralizumab, were approved by Health Canada. However, access to these therapies is extremely limited due to their high cost and stringent funding criteria. All of the therapies in use for NMOSD work by suppressing the immune system to prevent

relapses, with variable efficacy. Failure of treatment, with even just 1 relapse, can lead to a profound, permanent disability, including blindness and paralysis.

The clinician group input noted that there is a large unmet need for high-efficacy, well-tolerated therapies for NMOSD in Canada that have a significant impact on preventing and/or reducing relapses. Use of some of the off-label therapies is limited by many side effects, and many patients continue to have relapses despite treatment with drugs such as azathioprine and mycophenolate mofetil and, to a lesser extent, rituximab. Also, eculizumab is given by an IV infusion every 2 weeks, which is too onerous for some patients to tolerate.

According to the clinician group, the main treatment goals include the use of efficacious, safe and tolerable therapy immediately after the first episode to ideally avoid all future relapses, reduce the severity of relapses and the cumulative disability associated with them, and minimize AEs related to therapies. In particular, there is a major unmet need for patients who have a breakthrough relapse on their first therapy, as it can be challenging to identify a subsequent therapy that will be effective at preventing relapses and will be tolerated by the patient. The best approach for patients is to use as highly efficacious a product as possible after a relapse, so as to avoid potentially catastrophic subsequent relapses and thus optimize patient outcomes. The clinician group input noted that inebilizumab could be used as first-line treatment, and as subsequent treatments for patients who have had breakthrough relapses on other therapies or who were intolerant of other therapies. Inebilizumab would be expected to be used as a monotherapy based on the available clinical evidence and to avoid cumulative immunosuppressive effects. The clinician group also noted that although rituximab and inebilizumab both suppress B cells, there is some evidence that patients with polymorphisms in the *FCGR3A* gene may have an incomplete response to rituximab but not to inebilizumab. There is a lack of head-to-head data to compare inebilizumab and rituximab. The CNMSC also noted that there is no clear preferred drug among the novel monoclonal antibodies for the treatment of NMOSD (e.g., eculizumab, inebilizumab, ravulizumab, and satralizumab) and that the best mechanism of action may vary by patient. However, there is generally limited access to these therapies in Canada at this time.

According to the CNMSC, the key outcome measure is a new relapse episode, which is marked by new neurologic symptoms such as vision loss, weakness, sensory impairment, or dysfunction of the bladder or bowel. Although usually marked by a new enhancing lesion on MRI, this is not necessary to diagnose a relapse. The clinician group indicated that the drug renewal process should consider the occurrence of any relapse in the previous year and the number of relapses, EDSS or other disability measures, and any change from baseline (note that EDSS is not validated in NMOSD). The CNMSC recommended that the drug should be discontinued if the patient has a new relapse, a serious AE related to the therapy, or an EDSS score of 8 or higher.

The CNMSC stated that the treatment of patients with NMOSD should be assessed and managed by neurologists specialized in demyelinating diseases through an MS or demyelinating disease centre, and inebilizumab can be administered in a hospital or private clinic. Patients eligible for treatment with inebilizumab should have a confirmed diagnosis of NMOSD and a positive serum test for AQP4-IgG.

## Drug Program Input

Input was obtained from the drug programs that participate in the CADTH Reimbursement Review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for inebilizumab:

- relevant comparators
- considerations for the initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

**Table 2: Responses to Questions From the Drug Programs**

Implementation issues	Response
<b>Relevant comparators</b>	
<p>The N-MOmentum pivotal trial was a phase II/III multicentre, multinational, double-blind, randomized, placebo-controlled study.</p> <p>Is placebo an appropriate comparator, or should inebilizumab be compared with other therapies (such as eculizumab, satralizumab, ravulizumab, tocilizumab, rituximab, or other immunosuppressive treatments such as azathioprine, mycophenolate mofetil, or MTX) for maintenance treatment of NMOSD?</p>	<p>The clinical experts noted to CDEC that placebo was a reasonable comparator because at the time of the study initiation, the other monoclonal antibodies indicated for treatment of NMOSD (e.g., eculizumab, satralizumab, and others) were not available, and there were no other targeted disease-modifying therapies with an indication for NMOSD. The remaining therapies, such as rituximab and immunosuppressive treatments, are used off-label. Additionally, the immunosuppressive agents 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.</p> <p>CDEC noted that although the logistics of a comparative trial may have been challenging, it is not unreasonable to suggest that comparative evaluation between inebilizumab, eculizumab, satralizumab, and ravulizumab for the treatment of adult patients with NMOSD should be generated.</p>
<p>Given that the N-MOmentum trial compares inebilizumab to placebo and is not compared to current standards of therapy, where would inebilizumab be placed in treatment? Should inebilizumab be considered as a last line of approved therapies? Do patients need to trial satralizumab first?</p> <p>The sponsor indicated that inebilizumab is expected to have a place in therapy as an important new treatment option for patients who have experienced treatment failure with, or intolerance to, off-label immunosuppressive therapy (rituximab, azathioprine, or mycophenolate mofetil) in the same manner as</p>	<p>The clinical experts indicated to CDEC that patients with NMOSD should be able to access inebilizumab as a first-line or later-line therapy.</p> <p>The clinical experts also noted that patients should not be required to trial immunosuppressive therapies before accessing inebilizumab. The listed immunosuppressive treatments (rituximab, azathioprine, and 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</p>

Implementation issues	Response
<p>satralizumab. Do you agree with the proposed place in therapy?</p>	<p>underlying pathophysiology. As any relapse may have permanently disabling consequences, it is clinically inappropriate to require patients with this disease to trial ineffective therapies that have little evidence.</p> <p>The clinical experts also indicated that patients should not be required to trial satralizumab or eculizumab before accessing inebilizumab due to heterogenous inequitable issues with access to these therapies across Canada, and because different patients may have different responses to and/or preferences for the different targeted therapies now available for NMOSD. For example, the differences in infusion scheduling that may make some therapies inaccessible for practical reasons for some patients, especially those who are disabled, who live in a remote area, or who otherwise cannot manage the financial or travel burden to access infusion therapies frequently (e.g., every 2 weeks). Patients with NMOSD are more likely to be disabled and to experience unemployment because of their condition.</p> <p>CDEC noted that there is no evidence to define order of use between rituximab, inebilizumab, satralizumab, eculizumab, or ravulizumab, nor is there evidence for switching from 1 treatment to another.</p>
<p>Rituximab is used off-label for NMOSD, and its mechanism of action relates to inebilizumab. Given the similarity in the mechanism of action and lack of head-to-head trials between rituximab and inebilizumab, would using rituximab instead of inebilizumab be more cost-effective and achieve a similar response?</p>	<p>The clinical experts indicated that due to a lack of head-to-head data and very uncertain indirect data, it is unknown how the efficacy and safety of inebilizumab compares to rituximab. However, based on the differences in mechanism of action, inebilizumab (anti-CD19) is associated with a broader immunosuppression than rituximab (anti-CD20) due to targeting B cells earlier in their evolution, and so it is expected to be theoretically more effective than rituximab. Additionally, rituximab has very limited clinical evidence for the treatment of NMOSD, while there are phase III data supporting the efficacy of inebilizumab for this condition. Given the severity of the disease, even 1 episode may be permanently disabling; ergo, it may be considered inappropriate to use rituximab in place of inebilizumab.</p> <p>The clinical experts also 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 <i>FCGR3A</i> gene (F158) may have an incomplete response to rituximab (anti-CD20) but not to inebilizumab (anti-CD19).</p> <p>CDEC noted that there is no direct evidence comparing rituximab to inebilizumab, and the indirect comparison to rituximab could not be interpreted due to limitations in the analysis inherent to the data available, as well as sparsely reported methodology and results and inappropriate methodological decisions.</p>
Considerations for initiation of therapy	
<p>The SAKuraSky and SAKuraStar trials that assessed the efficacy and safety of satralizumab enrolled patients with an EDSS score of <math>\leq 6.5</math> points, while the N-MOMentum trial that assessed the efficacy and safety of inebilizumab enrolled patients with an EDSS score of <math>\leq 7.5</math> (with potential to include patients with a score of 8). This difference in EDSS score will result in a larger population that would be eligible for treatment, which needs to be considered.</p>	<p>This was a comment from the drug programs to inform CDEC deliberations.</p>

Implementation issues	Response
<b>Considerations for continuation or renewal of therapy</b>	
<p>One of the methods used to diagnose NMOSD is MRI. Will this be needed for reassessment for renewal of therapy? This may pose a limitation for access to patients.</p>	<p>The clinical experts indicated to CDEC that MRI would not be needed for initiation or reassessment of therapy and that it is not routinely conducted in the management of NMOSD.</p>
<b>Considerations for discontinuation of therapy</b>	
<p>What parameters are to be assessed to monitor for loss of response, absence of clinical benefit, or disease progression?</p>	<p>The clinical experts indicated to CDEC that frequency, severity, and recovery from NMOSD relapse episodes are the primary metrics of efficacy. It should be noted that a single relapse does not necessarily indicate drug failure, as targeted therapies such as inebilizumab may also result in fewer relapses, milder relapses, or better recovery from relapses, even if they are not completely prevented. Additionally, efficacy should not be evaluated before completing 6 months of treatment with inebilizumab. Ergo, patients should not necessarily discontinue treatment as a result of a single NMOSD relapse, and not due to relapses occurring in the first 6 months of treatment. Similarly, hospitalization may not necessarily be informative with regard to relapse severity, as hospitalization may be required for standard treatment of relapses (e.g., plasmapheresis).</p>
<p>The satralizumab recommendation for discontinuation is an EDSS score of 8 or higher. Should inebilizumab follow the same criteria?</p>	<p>The clinical experts noted to CDEC that inebilizumab should be discontinued if a patient reaches an EDSS score of 9, and this should be a medical decision rather than a coverage decision due to the complexities of measuring disability in patients with NMOSD.</p> <p>The clinical experts further noted that EDSS is not validated in NMOSD and has general weaknesses even in the measurement of MS-related disability, as it focuses primarily on ambulation as a measure of disability; for patients with NMOSD, it is particularly insensitive to other types of paralysis and losing visual acuity. A patient with an EDSS score of 8 would use a wheelchair but may otherwise still be independent in day-to-day life, and future NMOSD relapses could cause a loss of independence and/or result in losses in visual acuity or permanent blindness, which are clinically important outcomes to prevent.</p> <p>CDEC recommended that reimbursement of inebilizumab treatment should be discontinued if the patient's EDSS score is higher than 8.</p>
<b>Considerations for prescribing of therapy</b>	
<p>Treatment with inebilizumab involves the least frequent dosing compared to other therapies in this space. Would there be a more considerable uptake of inebilizumab vs. other drugs, such as satralizumab and ravulizumab?</p>	<p>The clinical experts noted to CDEC that greater uptake of inebilizumab is likely, due to the less frequent dosing schedule.</p>
<p>Who should prescribe inebilizumab? Is it neurologists, ophthalmologists, or others?</p> <p>How do patients living in remote areas access such specialties?</p>	<p>The clinical experts noted to CDEC that neurologists with experience or expertise in a related subspecialty should prescribe inebilizumab. Relevant subspecialties include MS neurology, neuroimmunology, autoimmune neurology, and neuro-ophthalmology. However, patients in remote areas may have issues with access to subspecialists. For patients living in remote areas, local neurologists without subspecialty expertise may work by distance in conjunction with neurologists who are experts in a relevant subspecialty.</p>

Implementation issues	Response
	<p>The clinical experts also noted that ophthalmologists should not prescribe inebilizumab, although they may be involved in the diagnosis of optic neuritis in patients with NMOSD.</p>
<p>Would you prescribe a combination of therapies if they have different mechanisms of action (i.e., eculizumab, ravulizumab, satralizumab)?</p>	<p>The clinical experts indicated that inebilizumab would not be combined with eculizumab, satralizumab, or other monoclonal antibodies for the treatment of NMOSD, due to higher risks and a lack of data.</p> <p>The clinical experts further noted that there could potentially be circumstances in which inebilizumab is combined with classical immunosuppressants such as azathioprine.</p> <p>CDEC recommended that due to a lack of evidence, inebilizumab should not be reimbursed when used in combination with rituximab, satralizumab, eculizumab, or ravulizumab.</p>
<p>Given that rituximab has a similar mechanism of action, would patients be eligible for inebilizumab (CD19 inhibitor) if they have already trialed rituximab (CD20 inhibitor)?</p>	<p>The clinical experts noted to CDEC that there are similarities in the mechanism of action between rituximab and inebilizumab as both target B cells. However, based on the differences in mechanism of action, inebilizumab (anti-CD19) is associated with a broader immunosuppression than rituximab (anti-CD20), due to targeting B cells earlier in their evolution, and so it is expected to theoretically be more effective than rituximab. Patients who experience treatment failure with rituximab may still see clinical benefit with inebilizumab due to these differences in mechanism.</p> <p>The clinical experts also 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 <i>FCGR3A</i> gene (F158) may experience an incomplete response to rituximab (anti-CD20) but not to inebilizumab (anti-CD19).</p> <p>CDEC noted that there is no evidence available for switching treatment from rituximab to inebilizumab.</p>
<b>Generalizability</b>	
<p>Would patients with optic neuritis benefit from inebilizumab?</p>	<p>The clinical experts noted to CDEC that inebilizumab is not expected to be used off-label in this population.</p>

CDEC = Canadian Drug Expert Committee; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorder; vs. = versus.

## Clinical Evidence

### Systematic Review

#### Description of Studies

One double-blind, randomized, placebo-controlled, phase II/III study (the N-MOMentum trial) was included in this review. The N-MOMentum trial comprised a 197-day randomized controlled period (RCP) and a single-arm, open-label period (OLP) with a minimum duration of 2 years. The N-MOMentum trial randomized 231 adult patients with NMOSD who had a documented history of either at least 1 acute NMOSD relapse in the prior year or at least 2 relapse episodes in the prior 2 years that required rescue therapy, and who had an EDSS score less than or equal to 7.5 (or 8.0 in special circumstances [i.e., if the investigator and

medical monitor assessed that the patient was reasonably able to complete the study]). EDSS is a measure of disability validated for use in patients with MS, but it has been applied to NMOSD due to the similarities in disability caused by these distinct conditions and the lack of an NMOSD-specific tool for assessing disease-related disability. EDSS scores range from 0 to 10, where 0 represents no disability, 9 represents a complete lack of independent mobility, and 10 represents death. The majority of patients were seropositive for AQP4-IgG, and subgroup data were available for the seropositive population. The primary end point was the time in days from day 1 to onset of an AC-determined NMOSD relapse on or before day 197. Key secondary end points included the proportion of patients with worsening in EDSS score from baseline to last visit during the RCP, change in low-contrast visual binocular score from baseline to last visit during the RCP, and the number of NMOSD-related inpatient hospitalizations during the RCP. Other secondary or exploratory outcomes included NMOSD relapse rate in inebilizumab-treated patients, safety outcomes, and HRQoL, using the Short Form (36) Health Survey (SF-36). Low-contrast binocular score was measured using the low-contrast Landolt C broken rings chart; scoring of this assessment is based on the number of characters on the chart that the patient is able to identify, from 0 to 70 (inclusive), where 70 indicates the patient was able to correctly identify all characters on the chart (i.e., best visual acuity score), and 0 indicates they were not able to identify any characters correctly (i.e., poorest visual acuity score). The SF-36 is a generic HRQoL questionnaire that yields a physical component score (PCS) and mental component score (MCS), in which higher scores represent better HRQoL.

At baseline, patients included in the N-MOMentum trial were mostly female (> 90%), had received prior acute or maintenance therapies for NMOSD (> 98%), were seropositive for AQP4-IgG (> 92%), and had a mean age of approximately 43 years. The median EDSS score at baseline was 4 in the placebo group (range, 1.0 to 8.0) and 3.5 in the inebilizumab group (range, 0.0 to 8.0); 29% in the placebo group and 24% in the inebilizumab group had an EDSS score of > 5 points at baseline.

## **Efficacy Results**

### ***NMOSD Relapses***

In the randomized period, among patients who were AQP4-IgG seropositive, treatment with inebilizumab (versus placebo) was associated with a 77.3% reduction in the risk of an AC-determined NMOSD relapse (Kaplan-Meier [KM] HR = 0.227; 95% CI, 0.1214 to 0.4232;  $P < 0.0001$ ). At day 197, a larger proportion of patients were relapse-free in the inebilizumab group (87.6%) than in the placebo group (56.6%). Treatment with inebilizumab likely results in a clinically important increase in the probability of having no relapse at day 197 compared to placebo.

Results were similar in the overall intention-to-treat (ITT) population and were also consistent across prespecified subgroups. Additionally, results were similar based on investigator-determined NMOSD relapses. During the RCP, among patients who were AQP4-IgG seropositive, 6 out of 18 relapses (33.3%) in patients treated with inebilizumab were considered “major” relapses, and 10 out of 22 relapses (45.5%) among patients treated with placebo were considered “major” relapses. Recovery from relapses was graded by the AC based on improvements in the relapse criteria. As a proportion of patients with relapses, “no attack recovery” was reported for 27.8% of patients in the inebilizumab group and 40.9% of patients in the placebo

group. Most relapses were myelitis (11 of 18 in the inebilizumab arm and 14 of 22 in the placebo arm), followed by optic neuritis (8 and 10, respectively), and few occurred in the brainstem (0 and 1, respectively). When calculated across the RCP and OLP, the annualized AC-determined NMOSD relapse rate in any patient treated with inebilizumab was 0.086 relapses per year in the total population and 0.09 relapses per year in the AQP4-IgG–seropositive population.

### ***Proportion of Patients With Worsening in EDSS Score***

During the RCP, among patients who were AQP4-IgG seropositive, treatment with inebilizumab likely resulted in a clinically important reduction in the proportion of patients who had worsening from baseline in EDSS compared to placebo at 197 days (odds ratio [OR] = 0.352 [95% CI, 0.1704 to 0.7252; P = 0.0047] ██████████ ██████████).

### ***Change From Baseline in Low-Contrast Visual Acuity Score***

The change in low-contrast visual acuity binocular score from baseline to the last RCP visit did not appear to differ by treatment group within the AQP4-IgG–seropositive population ██████████ ██████████. Based on these results, inebilizumab likely does not result in a clinically important difference in low-contrast visual acuity compared to placebo at 197 days.

### ***Number of NMOSD-Related Inpatient Hospitalizations***

██████████ ██████████. It was uncertain if the observed absolute difference was clinically meaningful because the 95% and 97.5% CIs both crossed the null, and the duration of the trial may have been insufficient to assess differences in NMOSD-related inpatient hospitalizations. The 95% CI of the relative difference (i.e., rate ratio), in contrast, did not include the null. The clinical experts consulted by CADTH indicated that any benefit would be clinically meaningful. In summary, inebilizumab may be associated with a benefit in this outcome but it is uncertain at the time frame assessed.

### ***Short Form (36) Health Survey***

During the RCP, among patients who were AQP4-IgG seropositive and treated with inebilizumab versus placebo, the mean change from baseline in the MCS was 1.066 (standard deviation [SD] = 9.581) versus 4.378 (SD = 7.017) at week 28, respectively. The mean change from baseline in the PCS was 0.710 (SD = 7.421) versus 0.364 (SD = 6.632) at week 28, respectively. No statistical test results were reported, but it was reported that there were no significant differences between treatment arms.

### ***Pain Numerical Rating Scale***

During the RCP, the mean changes from baseline to week 28 in the average pain score for all body locations were similar across treatment groups, and between the AQP4-IgG–seropositive and overall ITT populations. Similarly, the average pain scores for all body locations remained relatively constant during the OLP in the AQP4-IgG–seropositive and overall ITT populations, regardless of treatment assignment during the RCP. Treatment with inebilizumab likely results in no clinically meaningful change in pain numerical rating scale (NRS) from baseline to 28 weeks, relative to placebo.

## Harms Results

Nearly all patients who were AQP4-IgG seropositive experienced at least 1 AE during the study (71.2% of patients treated with placebo and 73.9% of patients treated with inebilizumab, respectively) and results were similar in the ITT subpopulation. Among patients who were AQP4-IgG seropositive, the rate of serious adverse events (SAEs) was 4.3% in the inebilizumab group and 11.5% in the placebo group during the RCP. Over the entire duration of the study, 20.4% of patients who received any dose of inebilizumab experienced an SAE. Withdrawals due to AEs were uncommon; including both the RCP and OLP, withdrawals due to AEs occurred in 1 patient receiving placebo only (who was AQP4-IgG seropositive), and in 4 patients who received inebilizumab (of which 3 were AQP4-IgG seropositive and 1 was AQP4-IgG seronegative). There were no deaths during the RCP. During the entire study, among patients treated with any dose of inebilizumab, 3 patients died due to NMOSD, pneumonia, and COVID-19 pneumonia (1 case each).

In the RCP, among patients who were AQP4-IgG seropositive, 50.0% in the placebo group and 49.1% in the inebilizumab group experienced at least 1 treatment-emergent adverse event (TEAE) of special interest, most commonly infections (44.2% and 40.4%, respectively), followed by infusion-related reactions (9.6% and 9.3%, respectively), hepatic function abnormality (3.8% and 5.0%), and cytopenia (0% and 5.0%). Results were similar in the overall ITT population.

During the OLP, among patients who were AQP4-IgG seropositive, most patients experienced at least 1 TEAE of special interest (85.1% in the placebo-to-inebilizumab group and 71.4% in the inebilizumab-to-inebilizumab group). Similar to the RCP, the most common TEAE of special interest was infection, followed by infusion-related reaction, hepatic function abnormality, and cytopenia. In addition, a few patients experienced hypersensitivity (0% and 1.3%, respectively) and [REDACTED]. Again, results were similar in the overall ITT population. Infections that occurred were generally mild and did not lead to treatment discontinuation in the OLP or RCP. However, higher rates of infection were observed during the OLP versus the RCP, which may be related to the prolonged duration of treatment and follow-up. Cytopenias were more common in patients treated with inebilizumab, which is consistent with inebilizumab's mechanism of action and class effects of B-cell depletion.

## Critical Appraisal

The N-MOmentum phase II/III trial was the only study included in this review. The N-MOmentum trial included an initial period that was randomized, placebo-controlled, and double-blind, with a duration of up to 197 days (the RCP), in which patients received inebilizumab 300 mg IV or placebo IV on day 1 and day 15. Patients could proceed to an open-label, single-arm period (the OLP), with a minimum duration of 2 years, during which patients received inebilizumab 300 mg IV every 6 months, starting from 6 months after the first infusion. In the RCP, there were no major concerns with regard to internal validity related to study design (e.g., method of randomization, concealment of allocation, maintenance of blinding, and balance of patient characteristics between treatment arms). As the trial was stopped early – based on the recommendation of the independent data monitoring committee (IDMC) that efficacy of inebilizumab had been established, so there was no justification to keep exposing patients to placebo – there may be a risk of overestimating the

true effect due to a slightly low information fraction (40 of 67 planned NMOSD relapse events in the AQP4-IgG-seropositive subpopulation). The end points in the trial were appropriately defined and were considered important to patients and clinicians, according to group inputs and clinical expert consultation. There was a high number of censored patients in the primary outcome of time to first NMOSD episode, especially in the inebilizumab treatment arm. However, this was considered unlikely to introduce bias because of the low number of early withdrawals and was considered likely to be due to the early cessation of the trial and the high proportion of relapse-free patients at day 197. The key secondary outcome of change in EDSS score was an appropriate and important outcome, but the EDSS has some weaknesses, including overreliance on ambulation as a metric of disability, and lower sensitivity to change in other types of disability at some ranges in the scale. EDSS is validated in MS but has not been validated in NMOSD. However, there are no superior scales for measuring disability in this population.

The eligibility criteria and baseline patient characteristics of the N-MOmentum trial were considered by the consulted clinical experts to be a reasonable approximation of patients with NMOSD in clinical practice in Canada, with the minor exception that some patients excluded for concomitant immunosuppressive or steroid therapy or prior IVIG would potentially be candidates for inebilizumab in real-world practice. All aspects of treatment management, including the steroid taper, rescue therapy, and preinfusion medications, adequately reflected clinical practice, according to the clinical experts. The N-MOmentum trial had a high proportion of screen failures (236 screen failures in 467 screened patients), and only 5 of these were due to the early cessation of the study. The clinical experts consulted by CADTH indicated that approximately one-third of the screen failures were due to tuberculosis testing, due to the global nature of the study, which would be expected to be lower in clinical practice in Canada. As such, the CADTH team considered this not to be a major concern for generalizability.

### **GRADE Summary of Findings and Certainty of the Evidence**

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- time to first NMOSD episode (assessed in GRADE as probability of no relapse at day 168 and 197)
- disability (proportion with worsening in EDSS score)
- low-contrast visual acuity (change from baseline to last visit in)

- number of NMOSD-related inpatient hospitalizations
- HRQoL (SF-36 mean change from baseline)
- pain NRS (mean change from baseline)
- proportion of patients with SAEs.

**Table 3: Summary of Findings for Inebilizumab Versus Placebo for Patients With AQ4P-IgG-Seropositive NMOSD in the N-MOMentum Trial**

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	New drug	Difference		
<b>Time to AC-determined NMOSD relapse</b>							
Proportion of patients with no relapse (by AC) during randomized controlled period Follow-up: Day 169	213 (1 RCT)	NR	592 per 1,000 patients	901 per 1,000 patients (840 to 939)	309 more per 1,000 patients (162 more to 455 more)	Moderate <sup>a</sup>	Inebilizumab likely results in a clinically important increase in the probability of having no relapse at day 169 compared to placebo.
Proportion of patients with relapse (by AC) during randomized controlled period Follow-up: Day 197	213 (1 RCT)	KM HR for time to first relapse = 0.227 (0.1214 to 0.4232)	566 per 1,000 patients	876 per 1,000 patients (810 to 920)	310 more per 1,000 patients (158 more to 461 more)	Moderate <sup>a</sup>	Inebilizumab likely results in a clinically important increase in the probability of having no attack at day 197 compared to placebo.
<b>Worsening in EDSS score</b>							
Proportion with worsening from baseline in EDSS Follow-up: Last visit (up to day 197)	213 (1 RCT)	OR = 0.352 (0.1704 to 0.7252)	346 per 1,000 patients	149 per 1,000 patients (94 to 204)	197 fewer per 1,000 patients	Moderate <sup>b</sup>	Inebilizumab likely results in a clinically important reduction in the proportion of patients who have worsening from baseline in EDSS compared to placebo at 197 days.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	New drug	Difference		
<b>Visual acuity</b>							
Change from baseline in low-contrast visual acuity score Follow-up: Last visit (up to day 197)	213 (1 RCT)	NR	Observed mean = 0.846; SE = 1.405 LS mean = 0.600; SE = 0.999	Observed mean = 0.481; SE = 0.486 LS mean = 0.562; SE = 0.572	LS mean difference = -0.038 (-2.3122 to 2.2357)	Low <sup>c</sup>	Inebilizumab may not result in a clinically important difference in low-contrast visual acuity compared to placebo at 197 days.
<b>Number of NMOSD-related inpatient hospitalizations</b>							
Number of patients with NMOSD-related inpatient hospitalizations Follow-up: 197 days	213 (1 RCT)	RR = 0.291 (0.1054 to 0.8017)	7 of 52 patients with a mean of 1.4 events (SD = 0.8) and median of 1 (range, 1 to 3) event	9 of 161 patients with a mean of 1.0 events (SD = 0.0) and median of 1 (range, 1 to 1) event	0.37 fewer hospitalizations 	Low <sup>d</sup>	Inebilizumab may result in a reduction in NMOSD-related inpatient hospitalizations compared to placebo over 197 days.
<b>HRQoL</b>							
SF-36 mean change from baseline Follow-up: Week 28	133 (1 RCT)	NR	Mental CS: 3.303; SD = 9.372 Physical CS: 0.364; SD = 6.632	Mental CS: 1.719; SD = 8.057 Physical CS: 0.710; SD = 7.421	NR	NA <sup>e</sup>	The effect of inebilizumab on HRQoL cannot be determined.
<b>Pain NRS</b>							
Pain NRS mean change from baseline Follow-up: Week 28	213 (1 RCT)	NR	Observed mean = 0.514; SE = 0.304 LS mean: 0.567 (0.229)	Observed mean = 0.296; SE = 0.119 LS mean: 0.279 (0.130)	LS mean difference = -0.288 (-0.8080 to 0.2318)	Moderate <sup>f</sup>	Inebilizumab likely results in no clinically meaningful difference in the change in pain NRS from baseline compared to placebo at 28 weeks.
<b>Harms</b>							
Proportion of patients with SAEs during	213 (1 RCT)	NR	115 per 1,000 patients (NR)	43 per 1,000 patients (NR)	72 fewer per 1,000 patients (NR)	Moderate <sup>g</sup>	Inebilizumab likely results in a lower proportion of patients with

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	New drug	Difference		
the randomized period							SAEs at 197 days compared to placebo. There is some uncertainty about the clinical importance of the estimates.

AC = adjudication committee; CI = confidence interval; CS = component score; EDSS = Expanded Disability Status Scale; HR = hazard ratio; HRQoL = health-related quality of life; KM = Kaplan-Meier; MID = minimal important difference; NA = not applicable; NMOSD = neuromyelitis optica spectrum disorder; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; RR = rate ratio; SAE = serious adverse event; SD = standard deviation; SE = standard error; SF-36 = Short Form (36) Health Survey.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

\*Rated down 1 level due to early cessation of the trial. Relatedly, there was a high degree of censoring that was imbalanced between treatment arms. However, the reasons for censoring did not appear concerning, so the CADTH review team judged that it was not likely to present an additional serious concern for bias, ergo it was not rated down a second time. No threshold of importance could be determined and the experts consulted by CADTH indicated that any benefit is clinically important, so potential benefits and harms were determined relative to the null value.

\*No minimally important between-arm difference could be established so the optimal information size approach was used to rate down 1 level in imprecision.

\*Rated down 2 levels for very serious imprecision because the CI included both potential benefit and potential harm. No MID was identified so potential benefits and harms were determined relative to the null value.

\*Rated down 1 level for serious imprecision because the CI included both potential benefit and potential harm. No threshold for clinically important differences was identified and the experts consulted by CADTH indicated that any benefit is clinically important, so potential benefits and harms were determined relative to the null value. The time frame of the study may be inadequate to determine a clinically meaningful difference in hospitalizations over a patient's life, so the certainty was rated down 1 additional level for indirectness.

\*No 95% CIs or between-group differences were reported for the SF-36.

\*Rated down 1 level for serious imprecision because the CI included both potential benefit and potential harm. No minimally important difference was established, so potential benefits and harms were determined relative to the null value. Note that this outcome was not controlled for multiple comparisons.

\*Rated down 1 level for serious concerns regarding imprecision; no 95% CI of the difference was available, so the optimal information size approach was used to judge imprecision. No minimally important threshold of difference was established, but the CADTH review team judged that the effect estimate might include an important between-group difference.

Source: Details included in the table are from the sponsor's Summary of Clinical Evidence and from sponsor responses to additional information requested by CADTH.

## LTE Studies

No LTE studies were submitted to CADTH.

## Indirect Comparisons

### Description of Studies

The sponsor-submitted ITCs included comparisons against satralizumab and eculizumab using published study data and MAIC methodology to adjust for between-trial differences, and a comparison against rituximab using IPD. Other therapies (azathioprine and mycophenolate mofetil) were also of interest and were included in the study selection criteria, but ITCs against these therapies were ultimately not considered feasible. Additionally, there was a published network meta-analysis (NMA) comparing eculizumab to satralizumab and inebilizumab, which was summarized briefly for comparison but not formally assessed.

### Efficacy Results

In the sponsor-submitted anchored MAICs, the result for time to NMOSD relapse was assessed comparing inebilizumab to each of satralizumab monotherapy and eculizumab. The results of the indirect comparison

between inebilizumab and satralizumab were inconclusive due to wide 95% CIs that crossed the null value and suggested imprecision (HR = 0.666 [95% CI, 0.182 to 2.435]). The risk of NMOSD relapse trended toward being higher with inebilizumab than with eculizumab (HR = 3.947 [95% CI, 0.917 to 17.0]), which agreed with the published NMA in terms of the direction of effect.

The sponsor also submitted unanchored IPD analyses comparing inebilizumab to rituximab for the outcomes of annualized attack rate (AAR) and EDSS. For AAR, the results lacked 95% CIs and could not be interpreted due to missing critical information in the reporting of methodology and results. For EDSS, no relative effect estimates were reported so the results could not be interpreted.

### **Harms Results**

No harms outcomes were assessed in the ITCs.

### **Critical Appraisal**

In the MAICs comparing inebilizumab to satralizumab monotherapy and eculizumab, there was unresolved between-trial heterogeneity with respect to patient populations and outcome definitions that were not mitigated by the MAIC methodology. Additionally, the factors selected for adjustment were not informed by clinical expert opinion or literature regarding important treatment effect modifiers in NMOSD. The MAICs may have been overadjusted for clinically unimportant factors that were selected in an inappropriate manner, without consultation of literature or clinical expert opinion, based only on statistical analysis of the N-MOmentum trial. The results of both comparisons had wide 95% CIs, suggesting substantial imprecision in the effect estimates, as well as small effective sample sizes, resulting in the effects being overly influenced by small subgroups of patients and highlighting poor overlap.

The submitted methodology for the MAIC analyses of inebilizumab versus rituximab are insufficient for critical appraisal. The 4 studies informing the rituximab data were small observational studies ( $N \leq 32$ ) in geographic regions that likely differ from Canada in terms of demographics and clinical practice. The sponsor noted that it was not feasible to conduct ITCs comparing to other off-label treatments such as azathioprine and mycophenolate mofetil due to small sample sizes and observational study designs. However, the same limitations exist for the available rituximab data, and the use of the MAIC methodology cannot correct for these limitations. Despite having access to the IPD for the rituximab studies, the sponsor-submitted MAICs only adjusted the N-MOmentum data to reflect the populations treated with rituximab, which are less similar to the population in Canada. Additionally, no relative effect estimates were reported for EDSS, and no 95% CIs were reported for AAR. There was no justification provided for why the sponsor selected single-arm observational studies to inform the ITCs instead of using an available published, placebo-controlled, double-blind, randomized trial comparing rituximab to placebo in AQP4-IgG-seropositive NMOSD. No conclusions can be drawn from the indirect comparisons to rituximab.

In all of the submitted MAICs, the submitted technical reports were missing critical details of the methods and results, which limited our ability to appraise the evidence and raised concerns about the validity of the analyses.

No safety-related outcomes were assessed.

There are no direct or indirect data available for the efficacy and safety of inebilizumab compared to azathioprine, mycophenolate mofetil, or ravulizumab.

## Studies Addressing Gaps in the Evidence From the Systematic Review

No additional studies were submitted to CADTH.

## Economic Evidence

### Cost and Cost-Effectiveness

**Table 4: Summary of Economic Evaluation**

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with NMOSD who are AQP4-IgG seropositive
Treatment	Inebilizumab
Dise regimen	300 mg at weeks 1 and 3, followed by 300 mg every 6 months (beginning with the first dose)
Submitted price	Inebilizumab, 10 mg/mL: \$25,623 per 10 mL vial
Treatment cost	\$153,738 per year
Comparators	Best-supportive care: no active therapy Rituximab Eculizumab Satralizumab
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (60 years)
Key data sources	N-MOmentum trial Sponsor-submitted ITCs
Key limitations	<ul style="list-style-type: none"> <li>The CADTH clinical review concluded that inebilizumab offered a meaningful benefit over BSC, but not when compared to eculizumab, in terms of TTAA. Conclusions could not be drawn for the comparison of inebilizumab relative to satralizumab or rituximab, as estimates of relative efficacy were not comparable due to the use of independent, pairwise ITCs for these comparators.</li> <li>The methods used to estimate state membership did not reflect best practices for Markov models. This resulted in a cohort simulation that failed to properly incorporate general population mortality as a competing risk in model transitions, and did not always consider the correct treatment-specific risk of an NMOSD relapse.</li> </ul>
CADTH reanalysis results	CADTH was unable to address the identified limitations of the submitted economic evaluation through reanalysis. A CADTH base case could therefore not be specified. The cost-effectiveness of inebilizumab in adults with NMOSD who are AQP4-IgG seropositive is unknown relative to all included comparator treatments.



AQP4-IgG = immunoglobulin G autoantibodies for aquaporin 4; BSC = best-supportive care; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; LY = life-year; NMOSD = neuromyelitis optica spectrum disorder; PSM = partitioned survival model; QALY = quality-adjusted life-year; TTAA = time to first adjudicated attack.

## Budget Impact

CADTH identified 2 key limitations with the sponsor's budget impact analysis. First, the prevalence of NMOSD in the population across Canada was underestimated. Second, the use of blended treatment costs led to uncertainty in the total treatment costs. The CADTH reanalysis involved updating the prevalence of NMOSD to 4.4 per 100,000 people. Results from the CADTH base case indicated that reimbursement of inebilizumab for the treatment of adults with NMOSD who are AQP4-IgG seropositive would be associated with a budgetary increase of \$3,309,644 in year 1, \$4,302,566 in year 2, and \$4,915,632 in year 3. The 3-year net budget impact was estimated to be \$12,527,843.

## CDEC Information

### Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunskey, Dr. Edward Xie, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Trudy Huyghebaert, Dr. Danyaal Raza, and Dr. Peter Zed.

**Meeting date:** January 25, 2024

**Regrets:** One expert committee member did not attend.

**Conflicts of interest:** None



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