Canada's Drug Agency
L'Agence des médicaments du Canada

March 2025

Drugs Health Technologies Health Systems

Reimbursement Recommendation

Cladribine and Natalizumab for Relapsing-Remitting Multiple Sclerosis

Streamlined review
Requester: Public drug programs
Final recommendation

Summary

The Formulary Management Expert Committee (FMEC) recommends that cladribine monotherapy or natalizumab monotherapy be reimbursed for the first-line treatment of patients with relapsing-remitting multiple sclerosis (RRMS), provided certain conditions are met.

FMEC reviewed a Cochrane systematic review with network meta-analysis (Gonzalez-Lorenzo et al. [2024]), identified by the Canada's Drug Agency (CDA-AMC) systematic review of the literature. This network meta-analysis is the most comprehensive and up-to-date synthesis of direct and indirect evidence from clinical trials of different treatments for RRMS published by an academic group. FMEC also considered input received from external partners, including MS Canada, the Canadian Network of Multiple Sclerosis Clinics (CNMSC), Biogen, EMD Serono, and public drug programs.

FMEC concluded that cladribine and natalizumab are more effective than the majority of lower efficacy disease-modifying treatments (DMTs) in reducing the frequency of relapses over 2 years of treatment. Although there is some uncertainty in the clinical value of the efficacy and safety, FMEC concluded that both cladribine and natalizumab address important unmet clinical needs that are not being met by treatment options currently reimbursed in the first-line setting of RRMS (i.e., B-cell therapies).

Based on publicly available list prices, the reimbursement of cladribine and natalizumab as first-line treatments for RRMS is generally expected to increase overall drug acquisition costs compared with all other first-line treatments reimbursed for RRMS, except for peginterferon beta-1a.

Therapeutic Landscape

What Is RRMS?

Multiple sclerosis (MS) is the most common autoimmune disorder of the central nervous system. It is a chronic inflammatory disease that causes neurological disability throughout adult life. Approximately 90% of persons living with MS in Canada are initially diagnosed with RRMS, which is characterized by unpredictable episodes of flare-ups (called *relapses*) followed by periods of stability or improvement (called *remissions*).

What Are the Current Treatment Options?

MS remains an incurable disorder. The most important goal of therapy is prevention of neurological disability. Effective DMTs can delay the occurrence of disease complications and the development of disability.

Presently, there are 2 approaches to treatment. The traditional escalation approach involves initiating treatment with DMTs with relatively favourable safety profiles but with only low to moderate efficacy and lower costs and then escalating to more effective DMTs based on continued disease activity and inadequate symptom control. An alternative approach is early intensive or high-efficacy treatment, which involves starting treatment with a higher efficacy DMT that may have less favourable safety profiles and higher costs. Historically, the escalation approach has been used, with high-efficacy DMTs reserved for patients with poor response to a traditional first-line (lower efficacy) drug. More recently, there has been a paradigm shift in the treatment for RRMS, whereby early intensive or high-efficacy treatment is preferred, with the goal to achieve disease control rapidly to minimize neurological damage and risk of disability worsening.

Why Did We Conduct This Review?

Natalizumab and cladribine are 2 high-efficacy DMTs used for the treatment of RRMS. Public reimbursement of these drugs is currently restricted to later lines of therapy after a lack of response or intolerance to lower efficacy DMTs.

There is growing evidence suggesting that early treatment with high-efficacy DMTs leads to better outcomes. There are 2 high-efficacy DMTs currently reimbursed as first-line treatment of RRMS, ocrelizumab and ofatumumab, which share similar mechanisms of action. However, clinicians who treat MS and patients living with the disease have both expressed a need for more treatment options for the first-line treatment of RRMS that have different mechanisms of action and modes of administration for patients with different treatment needs.

Input From Community Partners

- **MS Canada** reiterated the increasing shift to treat people with highly active MS with high-efficacy DMTs as soon as possible to minimize irreversible neurological damage and disability caused by suboptimal management of disease activity. MS Canada also highlighted the need for high-efficacy DMTs with different mechanisms of action to address the variability of disease presentation, response to DMTs, and patient treatment needs.

- **CNMSC** noted that having a range of treatment options for select patients, including those with aggressive disease, is critical to providing optimal care and avoiding serious disability. They also emphasized that achieving disease control as quickly as possible results in mitigation of disability and/or worsening disease in the long term, which benefits health outcomes in persons living with MS, as well as direct (i.e., health system) and indirect (i.e., productivity, social assistance) costs.
- **Biogen** and **EMD Serono** provided input in support of this Reimbursement Review. Biogen agreed that the project scope would be useful in decision-making and highlighted that there is no prespecified definition for highly active MS. EMD Serono emphasized the importance of timely recommendations following this review.
- **Public drug programs** provided input, highlighting implementation questions related to treatment eligibility and reimbursement criteria.

Note that considering the input we received on the project scope, and in consultation with the clinical experts, the review protocol was amended after posting the project scope to incorporate the broader RRMS population.

► **Refer to the main report and the supplemental material document** for this review.

Person With Lived Experience

Two People With Lived Experience shared their journeys of living with RRMS and their experiences with current treatment options. They shared the challenges of managing the disease with early DMTs, including side effects and the financial burden of treatments. Both emphasized the importance of early access to effective treatments to prevent irreversible damage and improve long-term outcomes. They also highlighted the significant costs beyond medication, including lifestyle adjustments, barriers related to employment, and home modifications required to accommodate their needs. They stressed the need for broader access to affordable treatments and underscored that MS is a highly individualized disease, and the need for access to a variety of treatment options to address the unique needs of each person with RRMS is crucial.

Deliberation

FMEC deliberated using the following 5 domains of value:

1. **Clinical value:** The value that patients derive from a health technology in terms of its effect on their health and health-related quality of life. The determination of the clinical value of a health technology

requires the measurement of its clinical benefits and harms and an assessment of the impact of these effects on patients. Clinical benefits and harms are assessed against relevant comparators.

2. **Unmet clinical need:** Morbidity and/or mortality arising from a condition or symptom that is not addressed effectively by available treatments.
3. **Distinct social and ethical considerations:** The social and ethical implications of health technologies not already assessed in the other domains and how they affect patients, caregivers, populations, and the organization of health systems. This includes nonclinical needs, which are the social, psychological, and logistical factors affecting the appropriateness, accessibility, and acceptability of the technology beyond its direct clinical outcomes. It also examines broader ethical considerations in the design, evaluation, and implementation of health technologies.
4. **Economic considerations:** Economic evidence to inform the financial, human, or other resource implications associated with the technology under review, and whether it is worthwhile to allocate resources to the technology under review given its expected clinical benefits. Considerations may include the potential resource or cost impacts of the technology under review versus relevant comparator(s).
5. **Impacts on health systems:** Two distinct but interrelated components — organizational feasibility of adoption is the ease with which the health technology can be implemented in the health system while realizing its clinical value and economic feasibility of adoption which examines how the adoption of a health technology will economically impact the payer or budget holder.

Decision Summary

Table 1 outlines the key discussion points FMEC considered, organized by the 5 domains of value.

Table 1: Summary of Deliberation

Domain	Discussion point(s)
Clinical value	**FMEC concluded that the clinical value of cladribine and natalizumab was uncertain for earlier use in the disease (i.e., in the first-line setting) versus relevant comparators in the Canadian setting.** **FMEC discussed the input from patient groups** and highlighted that key outcomes identified by patients are having early access to a range of high-efficacy drugs to reduce relapse and disability, addressing heterogeneity of disease activity, and placing patients at the centre of disease management. **FMEC members** highlighted the following discussion points: • FMEC noted that among other available high-efficacy treatment options with B-cell therapies, such as ocrelizumab and ofatumumab, natalizumab offers a different mechanism of action and cladribine also offers an oral treatment alternative. FMEC noted from discussion with guest specialists that B-cell therapies may not be suitable for patients with conditions such as inflammatory bowel disease or with severe immunodeficiency. • FMEC discussed the findings from the network meta-analysis that natalizumab and cladribine are more effective than all but 1 of the lower efficacy DMTs of interest (dimethyl fumarate) in reducing the frequency of relapses over 2 years of treatment. Using placebo as a common comparator, treatment with cladribine (RR = 0.53; 95% CI, 0.44 to 0.64; high-certainty evidence) and natalizumab (RR = 0.56; 95%

Domain	Discussion point(s)
	CI, 0.48 to 0.65; high-certainty evidence) resulted in a large decrease in the number of people who had MS relapses. FMEC noted that treatment with natalizumab or cladribine resulted in a larger decrease in the number of people who had MS relapses over 24 months compared with glatiramer acetate, interferon beta-1a and 1b, interferon beta 1a, interferon beta 1b, and teriflunomide. However, there were no data available for comparison with ocrelizumab and ofatumumab for this outcome. The lack of such data adds to the uncertainty in the clinical value of natalizumab and cladribine. • FMEC also discussed the limitation of the evidence with respect to the patient population of the studies included in the network meta-analysis. Most studies included either a mixed population of patients with and without previous treatment with DMTs or did not include data about previous treatment with DMTs. However, FMEC concluded that, overall, the evidence supports the first-line use of natalizumab and cladribine in RRMS. • FMEC also noted the different safety profiles of natalizumab and cladribine. The network meta-analysis showed no difference between treatment with natalizumab and with cladribine and other treatment comparators with respect to the number of people who experienced SAEs. However, FMEC discussed the heightened concern for PML with the use of natalizumab as well as mitigation strategies in place to minimize the risk of PML, such as monitoring the JCV titre. FMEC suggested that these drugs should be prescribed, and patients monitored, by those with experience in the treatment of MS.
Unmet clinical need	**FMEC concluded that there is significant clinical need that arises at early presentation of the condition despite available treatments (e.g., B-cell therapies) in the first-line setting and that natalizumab or cladribine may fill this need.** **FMEC discussed the input from patient groups** and highlighted that, to avoid unnecessary neurological damage and irreversible disability, patients want access to a range of high-efficacy medications soon after diagnosis. **FMEC members** highlighted the following discussion points: • FMEC highlighted that there has been a paradigm shift in the management of RRMS since the original reimbursement recommendations for cladribine (2018) and natalizumab (2009) were issued. FMEC also discussed the 2 treatment approaches for patients diagnosed with RRMS: the “escalation” approach versus an “early high-efficacy treatment” approach. There is a shift to adopt the “early high-efficacy treatment” approach in the management of MS, especially in patients with high disease activity, aggressive disease presentation, or rapidly evolving symptoms at onset because these patients are at significant risk of early worsening of disability. • FMEC heard from the guest specialists that natalizumab has been observed to have a faster onset of action in clinical practice. FMEC concluded that this may help meet an unmet clinical need. • FMEC discussed that the goal of therapy is to reduce the development of new lesions or relapses with progression to disability, morbidity, and mortality. • FMEC also noted that cladribine offers an oral route of administration, which is important for individuals who may not be candidates for parenteral therapy (e.g., needle aversion, difficult IV access) or may be at risk for nonadherence to parenteral therapy.
Distinct social and ethical considerations	**FMEC considered that cladribine and natalizumab may address some unmet nonclinical needs.** **FMEC discussed the input from patient groups** and highlighted that patients want access to a range of treatments that allow them to manage their disease based on their lifestyle, stage of life, preferences for mode of administration, and economic situation. **FMEC members** highlighted the following discussion points: • FMEC discussed that many high-efficacy drugs that are currently available in the first-line setting are administered intravenously or subcutaneously. These drugs may require additional resources (e.g., nursing monitoring, injection teaching support). Hence, the access of these resources may be restricted for individuals who are unable to access nearby health care facilities. The availability of an oral treatment option can bridge a treatment gap for patients who live in rural or remote areas (including Indigenous

Domain	Discussion point(s)
	communities) as well as those with needle aversion. • FMEC also noted some additional treatment considerations. For example, many treatment options are considered hazardous (teratogenic) and may be a barrier for family planning. Additionally, some treatments (e.g., natalizumab) are available through a controlled distribution program, in which patients must provide informed consent before treatment access and safety monitoring.
Economic considerations	**FMEC concluded that there are economic considerations that are important to address when implementing natalizumab or cladribine in the context of moving these therapies earlier in the treatment management.** **FMEC members** highlighted the following discussion points: • FMEC noted that, based on publicly available list prices, the reimbursement of natalizumab will result in increased drug acquisition costs compared with currently available high-efficacy DMTs (i.e., ocrelizumab and ofatumumab). The treatment duration for cladribine specified in its product monograph is 2 years; therefore, the annual cost of cladribine in those 2 years exceeds that of ocrelizumab and ofatumumab. However, overall differences in treatment acquisition costs are uncertain and will be dependent on comparative relapse rates and treatment durations, evidence for which was not available in this review. FMEC noted that if people who receive cladribine discontinue it after 2 years of treatment and do not reinitiate treatment with cladribine or another DMT, cladribine is likely to be less costly than ocrelizumab and ofatumumab after 2 years at public list prices because they would no longer be receiving a DMT. • No evidence was available to inform the comparative efficacy of natalizumab or cladribine to ocrelizumab or ofatumumab in terms of disease relapse. For other outcomes, including disability worsening over 24 months, treatment discontinuation due to adverse events and serious adverse events, results from the network meta-analysis suggest no difference between natalizumab or cladribine versus high-efficacy DMTs, including ocrelizumab and ofatumumab. As such, there is limited evidence to support a price premium for natalizumab or cladribine over ocrelizumab and/or ofatumumab (i.e., currently available high-efficacy DMTs). • FMEC discussed that there are generics for cladribine under review by Health Canada, although it is unknown whether the products under review are the oral or IV formulation. One biosimilar to natalizumab is currently under review. However, it is unknown when or if these generics and biosimilars will become available. FMEC noted that treatment acquisition costs associated with natalizumab and cladribine are likely to decrease if biosimilars and generics become available.
Impacts on health systems	**FMEC concluded that there are no additional impacts on health systems that are important to address when implementing cladribine or natalizumab earlier (i.e., first line).** **FMEC members** highlighted the following discussion points: • FMEC noted that cladribine will likely result in reduced demands on health care resources, while natalizumab may increase the demand for existing resources, mainly related to the IV administration of the medication. Both cladribine and natalizumab are currently available in the second-line setting of RRMS. Hence, existing health systems have established infrastructures to support their use.

CI = confidence interval; DMT = disease-modifying therapy or treatment; FMEC = Formulary Management Expert Committee; JCV = John Cunningham virus; PML = progressive multifocal leukoencephalopathy; RR = relative risk; RRMS = relapsing-remitting multiple sclerosis; SAE = serious adverse event.

Full Recommendation for Cladribine

With a vote of 8 to 0, FMEC recommends that cladribine, for the first-line monotherapy of RRMS, be reimbursed if the conditions presented in Table 2 are met.

Note that these conditions will supersede previous Canadian Drug Expert Committee (CDEC) recommendations issued on October 26, 2018 (Cladribine for Relapsing-Remitting Multiple Sclerosis [SR0546]).

Table 2: Conditions, Reasons, and Guidance for Cladribine Recommendation

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Patients must have the following characteristics at the time of initiating treatment with cladribine: 1.1. a diagnosis of RRMS established according to current clinical criteria including the MRI evidence.	The Cochrane systematic review and network meta-analysis (Gonzalez-Lorenzo et al. [2024]) suggest that cladribine is more effective than most lower efficacy drugs in preventing relapses at 2 years with no difference in disability worsening over 24 months compared with ocrelizumab or ofatumumab. Cladribine did not show a less favourable safety profile compared with other lower efficacy and higher efficacy first-line treatment options regarding common serious adverse events. As such, the previous reimbursement condition (i.e., to require prior use of another DMT) has been removed as long as the patient has a diagnosis of RRMS established according to current clinical criteria and MRI evidence.	At the time of the review, the most current diagnostic criteria for multiple sclerosis would be based on the 2017 McDonald Diagnostic Criteria. FMEC noted that the formal publication of the 2024 revised criteria was not yet released.
Discontinuation and renewal		
Not applicable.	The previous recommendation did not specify any discontinuation and renewal criteria.	FMEC noted that cladribine is prescribed as an induction treatment over 2 years, After the induction period is completed, the patient should be monitored per standard practice.
Prescribing		
2. Patients must be under the care of a specialist with experience in the diagnosis and management of MS.	This condition is as per previous recommendation. Additionally, this will ensure that appropriate treatment is prescribed for patients, and adverse events are optimally managed.	—
Pricing		
3. Cladribine should be priced so that it does not exceed the total drug program cost of treatment with the least costly high-efficacy DMT available for the first-line treatment of RRMS.	Based on the available network meta-analysis, no evidence was available to inform the effectiveness of cladribine compared with ocrelizumab or ofatumumab for relapses. For disability worsening over 24 months, treatment discontinuation due to adverse events and serious adverse events, results from the network meta-analysis suggest there is no	There are 2 high-efficacy DMTs currently reimbursed as first-line treatment of RRMS: ocrelizumab and ofatumumab.

Reimbursement condition	Reason	Implementation guidance
	difference between cladribine versus ocrelizumab or ofatumumab. As such, there is no evidence to support a price premium of cladribine over other high-efficacy DMTs available for the first-line treatment of RRMS.	

DMT = disease-modifying therapy or treatment; FMEC = Formulary Management Expert Committee; MS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis.

Full Recommendation for Natalizumab

With a vote of 8 to 0, FMEC recommends that natalizumab, for the first-line monotherapy of RRMS, be reimbursed if the conditions presented in Table 3 are met.

Note that these conditions will supersede previous CDEC recommendations issued on February 25, 2009 (Natalizumab for Relapsing-Remitting Multiple Sclerosis [SR0133]).

Table 3: Conditions, Reasons, and Guidance for Natalizumab Recommendation

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Patients must have the following characteristics at the time of initiating treatment with natalizumab: 1.1. a diagnosis of RRMS established according to current clinical criteria including the MRI evidence.	The Cochrane systematic review and network meta-analysis (Gonzalez-Lorenzo et al. [2024]) suggest that natalizumab is more effective than most low-efficacy drugs in preventing relapses at 2 years with no difference in disability worsening over 24 months when compared to ocrelizumab or ofatumumab. Natalizumab did not show a less favourable safety profile compared to other low-efficacy and high-efficacy first-line treatment options. As such, the previous reimbursement conditions (e.g., to require prior use of other DMT, significant increase in T2 lesion load and requiring 2 or more disabling relapses in the previous years) have been removed, as long as the patient has a diagnosis of RRMS established according to current clinical criteria.	FMEC notes that there is existing guidance in place to manage the risk of PML (e.g., monitoring of JCV at baseline and routinely during treatment). At the time of the review, the most current diagnostic criteria for multiple sclerosis would be based on the 2017 McDonald Diagnostic Criteria. FMEC noted that the formal publication of the 2024 revised criteria was not yet released.
Discontinuation and renewal		
Not applicable.	The previous recommendation did not specify any discontinuation and renewal criteria.	Based on discussion with guest specialists, FMEC notes that careful management is required after discontinuation of natalizumab to prevent the risk of rebound disease activity. There should be a plan to

Reimbursement condition	Reason	Implementation guidance
		transition to another DMT as soon as possible.
Prescribing		
2. Patients must be under the care of a specialist with experience in the diagnosis and management of MS.	This will ensure that appropriate treatment is prescribed for patients, and adverse events are optimally managed.	—
Pricing		
3. Natalizumab should be priced so that it does not exceed the total drug program cost of treatment with the least costly high-efficacy DMT available for the first-line treatment of RRMS.	Based on the available network meta-analysis, no evidence was available to inform the effectiveness of natalizumab compared with ocrelizumab or ofatumumab for relapses. For disability worsening over 24 months and treatment discontinuation due to adverse events and serious adverse events, results from the network meta-analysis suggest there is no difference between natalizumab versus ocrelizumab or ofatumumab. As such, there is no evidence to support a price premium of natalizumab over other high-efficacy DMTs available for the first-line treatment of RRMS.	There are 2 high-efficacy DMTs currently reimbursed as first-line treatment of RRMS: ocrelizumab and ofatumumab.

DMT = disease-modifying therapy; JCV = John Cunningham virus; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy; RRMS = relapsing-remitting multiple sclerosis.

Feedback on Draft Recommendation

One clinician group (Canadian Network of MS Clinics), 1 industry group (EMD Serano), and the public drug programs provided feedback on the draft recommendation. The Canadian Network of MS Clinics agreed with the recommendation and the reimbursement conditions for both cladribine and natalizumab. EMD Serano, as the manufacturer of the brand version of cladribine, supported the recommendation for cladribine. Both the clinician group and the industry group highlighted the health economic and cost considerations for the treatments of MS, emphasizing the costs for cladribine should reflect a longer duration to cover the period of disease remission following the induction treatment regimen. However, based on the evidence identified for this review, there was insufficient evidence available to inform a robust cost comparison over a longer time horizon. The clinician group was pleased that the review is based on a Cochrane systematic review of a network meta-analysis. The group also suggested that real-world evidence be integrated into the evidence evaluation processes. EMD Serano shared additional data related to the efficacy, safety, and health-related quality of life for cladribine. The public drug programs provided editorial comments that were incorporated where feasible.

FMEC Information

Members of the committee: Dr. Emily Reynen (Chair), Dr. Zaina Albalawi, Dr. Hardit Khuman, Ms. Valerie McDonald, Dr. Bill Semchuk, Dr. Jim Silvius, Dr. Marianne Taylor, Dr. Maureen Trudeau, Dr. Dominika Wranik, and 2 nonvoting guest specialists from Alberta and Ontario. Note that the guest specialists also acted as the clinical experts for the Clinical and Pharmacoeconomic Combined Report.

Meeting date: January 30, 2025

Conflicts of interest: None

Special thanks: CDA-AMC extends our special thanks to the individuals who presented directly to FMEC on behalf of people with lived experience and to patient organizations representing the community of those living with MS, particularly MS Canada, including Julie Kelndorfer, Barb Van Walleghem, Julia Nimilowich, and Jennifer McDonell.

Note: CDA-AMC makes every attempt to engage with people with lived experience as closely to the indication and treatments under review as possible; however, at times, CDA-AMC is unable to do so and instead engages with individuals with similar treatment journeys or experience with comparators under review to ensure lived experience perspectives are included and considered in Reimbursement Reviews. CDA-AMC is fortunate to be able to engage with individuals who are willing to share their treatment journey with FMEC.

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca