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

CDA-AMC REIMBURSEMENT REVIEW

Feedback on Draft Recommendation

cladribine & natalizumab

(Streamlined Drug Class Review)

Therapeutic area: Relapsing Remitting Multiple Sclerosis

Mar 6, 2025

CDA-AMC Open Calls for Input and Feedback

Draft Reimbursement Recommendation and Draft Report for "Cladribine and Natalizumab for Relapsing-Remitting Multiple Sclerosis"

Project number: TS0004-000; https://www.cda-amc.ca/cladribine-and-natalizumab-relapsing-remitting-multiple-sclerosis

Brand Name: Mavenclad and Tysabri

Generic Name: Cladribine and Natalizumab

Indication(s): Relapsing-remitting multiple sclerosis (RRMS), including Highly Active RRMS

Group Name: Canadian Network of MS Clinics (CNMSC)

Primary contact: Dr. Sarah Morrow

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Introductory comments from CNMSC

The Canadian Network of Multiple Sclerosis (MS) Clinics[1] (CNMSC; https://cnmsc.ca/) has been very committed to supporting Canada's Drug Agency's (CDA-AMC) evaluations in the areas of multiple sclerosis (MS) and other demyelinating diseases.

CNMSC is pleased to continue this support as CDA-AMC evaluates the comparative efficacy and harms of cladribine and natalizumab for first-line treatment of highly active RRMS via the FMEC process, to inform reimbursement of these 2 drugs.

Overall, CNMSC is pleased that FMEC has determined that cladribine and natalizumab should be reimbursed for the first line (1L) treatment of patients with RRMS based on specific criteria. More specific comments are provided below, with a focus on the Draft Recommendation and a few comments regarding the draft Review Report.

It is imperative that the outputs of this process are finalized and implemented by the jurisdictions as quickly as possible, to provide equitable access to these medications across the country and mitigate the serious negative impact/permanent disability associated with RRMS.

Specific comments on the draft recommendations

Outlined below are CNMSC's responses to the specific questions posed by the CDA-AMC input process.

1. **Are the draft recommendations presented in a clear manner (i.e., wording)? If not, how can the wording of the recommendations be improved for clarity?**
    a. **Cladribine**
        i. CNMSC agrees with the recommendation and associated reimbursement conditions outlined in Table 2/page 10 of the draft document.
        ii. CNMSC finds the recommendation clear and has no suggestions for changes.

[1] CNMSC is a national network of academic and community-based clinics established for the advancement of patient services, education, and research in MS.

b. Natalizumab

i. CNMSC agrees with the recommendation and associated reimbursement conditions outlined in Table 3/page 12 of the draft document.

ii. CNMSC finds the recommendation clear and has no suggestions for changes.

2. Will the draft recommendations be helpful to those making policy or clinical practice decisions?

a. CNMSC appreciates the time and effort put into reviewing the evidence available and devising updated and clinically relevant criteria for use.

b. CNMSC appreciates CDA-AMC's recognition of the changing paradigm in the approach to the treatment of MS and hopes that this translates into modernization in how jurisdictions provide reimbursement for products in MS more broadly.

c. One of the key recommendations that CNMSC made in its submission regarding the project scope was to summarizing costs over 2 timeframes: a) yearly costs; and, b) a 3 to 5-year time period, in order to enable more accurately compare costs associated with different regimens.

i. We note that Table 11 (page 29) of the Review Report does not address this suggestion and could leave policy makers with an inaccurate impression of the true costs associated with some of the regimens listed (particularly cladribine).

d. A key concern is how quickly the jurisdictions will move to update their own criteria to enable access by patients and prescribers in their individual provinces/territories. Anything that CDA-AMC can do to accelerate the process of translation from recommendation to actual patient access would be appreciated.

3. Has all the relevant evidence in the science report been taken into account in regard to these recommendations? If not, please explain why, citing evidence to support your position.

a. CNMSC is pleased that CDA-AMC integrated the Cochrane systematic review with network meta-analysis (Gonzalez-Lorenzo et al., 2024) into its review process. This review was a timely addition to the available evidence addressing the question at hand.

b. While we appreciate the focus on clinical trial evidence, we still believe that it is important for CDA-AMC to continue to look at how to more effectively integrate real-world evidence (RWE) into its evidence evaluation processes.

i. For example, some of the comments related to the durability of the effect of cladribine (Page 8, Economic Considerations) could have been addressed via the available long-term data.[2]

ii. This is a key policy question that cannot be addressed through traditional clinical trials (due to ethical considerations) yet could be more informed through RWE sources with appropriate caveats.

4. Please provide any additional comments you may have about this report.

a. CNMSC has appreciated the opportunity to participate in this process.

b. The process of reviewing evidence to address the policy question of 1L use of select therapies in RRMS started in February 2022. We believe it is important for CDA-AMC to generate best practices from this experience that can be applied to future projects, so as to ensure completion in support of timely access for Canadians.

[2] Giovannoni G, et al. Long-term follow-up of patients with relapsing multiple sclerosis from the CLARITY/CLARITY Extension cohort of CLASSIC-MS: An ambispective study. Multiple Sclerosis Journal. 2023 Apr 3:13524585231161494.

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	TS0004
Name of the drug and Indication(s)	cladribine and natalizumab, RRMS
Organization Providing Feedback	FWG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	X
	No requested revisions	☐

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification. Clarification is needed regarding the language of "highly active relapsing MS" and the expert opinions on MRI monitoring intervals, as well as additional contextual details pertaining to the off-label treatments addressed in the draft recommendations report and DPI, as well as the necessity of inclusion of the discussion around the third course of cladribine which may fall as out of scope for this review
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification. Additional contextual details and language around potential increase in drug acquisition costs due to the use of cladribine and natalizumab needs to be included, specifically how these drugs

compare with other first-line DMTs in terms of costs and efficacy, as well as the need for cost analysis to support these claims.
c) Implementation guidance
Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here. Additional details and language pertaining to unmet clinical needs for patients ineligible for higher efficacy treatments, along with clarification on the expert opinions regarding treatment cycles, monitoring frequency, and whether these treatments would lead to a demand for additional healthcare resources.

Outstanding Implementation Issues

In the event of a positive draft recommendation, drug programs can request further implementation support from CADTH on topics that cannot be addressed in the reimbursement review (e.g., concerning other drugs, without sufficient evidence to support a recommendation, etc.). Note that outstanding implementation questions can also be posed to the expert committee in Feedback section 4c.

Algorithm and implementation questions
1. Please specify sequencing questions or issues that should be addressed by CADTH (oncology only)
1. 2.
2. Please specify other implementation questions or issues that should be addressed by CADTH
1. 2.
Support strategy
3. Do you have any preferences or suggestions on how CADTH should address these issues?
May include implementation advice panel, evidence review, provisional algorithm (oncology), etc.