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

CDA-AMC REIMBURSEMENT REVIEW

Patient, Clinician and Industry Input

Cladribine and Natalizumab for Highly Active Relapsing-Remitting Multiple Sclerosis

(Streamlined Drug Class Review)

Sept 13, 2024

This document compiles the input submitted by patient groups, clinician groups, and industry for the file under review. The information is used by CDA-AMC in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings. **If your group has submitted input that is not reflected within this document, please contact Pharmaceuticals@cda-amc.ca.**

Disclaimer: The views expressed in this submission are those of the submitting organization or individual. As such, they are independent of CDA-AMC and do not necessarily represent or reflect the views of CDA-AMC. No endorsement by CDA-AMC is intended or should be inferred.

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MS Canada Input Related to the CDA's Streamlined Drug Class Review of Cladribine and Natalizumab for Highly Active Relapsing-Remitting Multiple Sclerosis

Project number: TS0004-000
Primary contact: Jennifer McDonell
Submitting organization: MS Canada
Date: September 12, 2024

CDA Policy Question: Should cladribine and natalizumab be reimbursed as first-line therapies in adult patients with highly active RRMS?

Research Questions:

1) *What is the clinical efficacy and safety of natalizumab and cladribine as first-line treatments in patients with highly active relapsing-remitting multiple sclerosis compared to drugs currently used as first-line treatment in adult patients with highly active RRMS?*

2) *How do costs compare across disease modifying therapies for the treatment of adult patients with highly active RRMS?*

MS Canada is an organization that provides information, support, and advocacy to Canadians affected by MS, and funds research to find the causes and cure for the disease. We work towards ensuring Canadians living with MS, and their families, can participate fully in all aspects of life. To do this we are focused on our impact goals including advancing treatment and care. We believe that Canadians living with MS have a right to access all Health Canada approved disease-modifying therapies (DMTs) as early intervention with the most appropriate medication is vital to avoid many of the long-term health, economic and personal costs that result from unnecessary irreversible disability. Their patient voice is central to the goals of eliminating or reducing symptoms, slowing, preventing, and ultimately curing the disease. This requires timely, equitable, affordable, and consistent access to the full array of approved treatments, ranging from longstanding compounds to more recently approved innovative agents because no two people have the same disease course or respond in the same way to the same medication. A central premise must include the concept of "the right medication at the right time", enabling Canadians living with MS, and those at the highest risk of developing MS, to benefit from those medications most appropriate for them regardless of where they live or their income status, and their patient voice is integral in this decision-making in collaboration with their healthcare team.

Unmet Treatment Needs

Our work includes a focus on the unmet treatment needs of Canadians with highly active relapsing MS, the focus of this current streamlined drug review. It is imperative for the Formulary Management Expert Committee (FMEC) work with clinicians using the existing evidence that was submitted and reviewed during the project that culminated in Canada's Drug Agency's report "Alemtuzumab, Cladribine,

MS Canada

Fingolimod, and Natalizumab as First-Line Treatments in Adult Patients with Highly Active Relapsing MS," in conjunction with the patient group, MS Canada to develop the criteria to ensure relevancy and expedited implementation. This subsequent review has the potential to support needed policy change, and provide MS clinicians, in collaboration with their patients, the opportunity to treat MS with the right medication, at the right time.

Current drug policy in Canada rarely allows people living with MS to initiate treatment with a high efficacy therapy because of the associated strict and limiting reimbursement criteria. Unfortunately, this criterion, shapes how clinicians are able to treat the disease, even in patients with a highly active disease course.

In Canada, the treatment of MS is largely dictated by reimbursement practices that follow an escalation approach, which is also based on limited evidence. Over the past two decades, there has been significant growth in our understanding of the pathophysiology of MS and as a result the development of innovative and highly effective therapeutic targets. Treatment approaches have not evolved to reflect these advancements in MS treatment and governments continue to use the escalation approach as the foundational framework around drug plan decision-making.

There is an increasing shift to treat people with highly active MS with high-efficacy DMTs as soon as possible to avoid unnecessary damage and irreversible disability caused by suboptimal management of disease activity. Integrally dependent on early and effective treatment of MS is its timely diagnosis. Delays in diagnosis and care of MS are not new within the Canadian healthcare system; however, the pandemic caused significant disruption to the access and availability of healthcare services[i]. The impact of this disruption has created a backlog of healthcare services which will further delay the diagnosis and treatment of MS for some Canadians who may have highly active disease. By the time they have received a diagnosis and initiated a treatment under the current reimbursement policy that mandates an escalation approach to treatment, they will have lost a potentially critical therapeutic window to preserve brain health and function. For people living with MS, time is brain.

There is a need for high efficacy DMTs with varied mechanisms of action to address the heterogeneity of the disease response to DMTs as well as place the patient at the centre of their disease management based on their lifestyle and stage of life.

Both the AAN[ii] and CMSWG[iii] guidelines are clear in their recommendations for initiating treatment with a high-efficacy DMT in people who present with high disease activity at the time of diagnosis as early as possible to avoid unnecessary damage and irreversible disability caused by suboptimal management of disease activity. Poor prognostic factors are well documented and can identify individuals with highly active disease so that optimal treatment can be initiated as early as possible within the critical therapeutic window to preserve brain health and function.

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Inadequate Research Questions
We do not feel that the current research questions in this review will adequately or appropriately address the policy question. Similarly, as we noted, in MS Canada's February 2022 submission in response to the initial Proposed Project Scope DR0087-000 we stated that patient reported outcomes and determinants of health were not addressed in the research question underpinning the proposed project scope.

As we have previously stated, in our March 2024 submission related to the CDA project number *HT0038-000: Alemtuzumab, Cladribine, Fingolimod, and Natalizumab as First-Line Treatments in Adult Patients with Highly Active Relapsing MS,* the lack of head-to-head comparison studies is a longstanding challenge in the pharmacoeconomic review of multiple sclerosis (MS) disease-modifying therapies for public payer decision-making.

There are no MS DMTs formally indicated as first-line treatments for individuals with "highly active relapsing MS", and the two RCTs that aim to address this, TREAT-MS and DELIVER-MS, are ongoing with expected completion dates within the following one to three years. Thus, MS Canada does not feel it is possible to adequately respond to the research questions, nor that they are the correct questions to ask for the review of 1L high efficacy DMTs for treatment of people with highly active relapsing MS. The research questions will not meaningfully address the current needs of this subpopulation of Canadians living with highly active relapsing MS and do not appear to reflect the spirit and intended goal of the FMEC from the perspective of a patient group.

MS is a Costly Disease
As a chronic disease of the central nervous system, MS often requires increased multidisciplinary care needs, limits the ability to participate in the workforce, and reduces quality of life. It is estimated that the annual cost of MS approximately $3.4 billion in Canada which is equivalent to an average annual cost of more than $42,880 per person.[iv]

MS significantly affects individuals' ability to work, leading to economic costs for them, their employers, and the government. Key areas of productivity loss include early retirement, frequent sick leave, reduced productivity while at work, loss of future income due to early death, and income loss for family members providing care. The government bears the largest share of these costs.

The average cost of an MS DMT ranges from approximately $7,000 CAD to more than $50,000 CAD per patient, per treatment year. Drug cost comparison must extend beyond the unit cost of the medication dose and dosing schedule.

Repercussions of suboptimal treatment can result in greater financial burden to health and social systems. Without access to early or effective treatment, individuals are at high risk of hospitalization due to acute disease exacerbations. The cost of a mild to moderate relapse is $7,275 (CAD) and a severe relapse is estimated to cost $17,458.[v] This does not account for loss of productivity costs and other indirect costs associated with increased and often irreversible disability. In Canada, the average cost of disease worsening per year in an individual living with MS with mild disability was estimated at $30,836, moderate disability was estimated at $46,622 per year and severe disability at $77,981.[vi] It is critical that

the CDR considers the costs associated with burden of disease in relation to the overall cost of the DMTs, as well as patient choice of each of the DMTs under review including mode of administration, mechanism of action, and dosing schedules. Health outcomes need to be inclusive of the broader social determinants of health and not limited to drug budgets.

Safety and Efficacy of Natalizumab and Cladribine

Phase 3 clinical safety and efficacy data of natalizumab and cladribine in relapsing-remitting MS fulfilled market authorization criteria by regulatory authorities globally and both possess extensive long-term safety and efficacy data. Natalizumab has long term safety and efficacy data spanning over a decade[vii], with more than 15 years of post-market utilization in Canada[viii]; and cladribine maintains over five years of real-world safety and efficacy data in people with HAMS.[ix]

Closing comments

MS Canada is pleased to continue to work collaboratively with the CDA, MS clinicians and most importantly, members of our MS community through their lived experience, to make positive policy change related to access to treatments for Canadians living with MS.

We have seen significant change over the past several years in our work with the CDA. We are committed to keeping the momentum of this work going to realize our end goal of universal coverage of the full range of Health Canada authorized medicines for MS with the flexibility to allow for different treatment approaches based on clinical presentation and treatment goals as discussed between the clinician and patient. This includes different classes of medications and administrations as the clinical response to each of these drugs will vary greatly from person to person based on their unique patient journey including disease type and course, stage of life, and personal choices driven by lifestyle, health, and economic factors.

This project has the opportunity to provide substantial evidence to support policy change, and provide MS clinicians, in collaboration with their patients, the opportunity to treat MS with the right medication, at the right time.

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[i] https://mscanada.ca/sites/default/files/documents/2023-10/deloitte-covid-19-impact-english_0.pdf

[ii] Rae-Grant A, Day GS, Ann Marrie R, et al. Comprehensive systematic review summary: disease-modifying therapies for adults with multiple sclerosis: report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. Neurology. 2018;90:789–800.

[iii] Freedman MS, Devonshire V, Duquette P, Giacomini PS, Giuliani F, Levin MC, Montalban X, Morrow SA, Oh J, Rotstein D, Yeh EA; Canadian MS Working Group. Treatment Optimization in Multiple Sclerosis: Canadian MS Working Group Recommendations. Can J Neurol Sci. 2020 Jul;47(4):437-455. doi: 10.1017/cjn.2020.66. Epub 2020 Apr 6. PMID: 32654681.

[iv] https://mscanada.ca/sites/default/files/documents/2023-10/deloitte-covid-19-impact-english_0.pdf

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[v] Baharnoori M, Bhan V, Clift F, Thomas K, Mouallif S, Adlard N, Cooney P, Blanchette F, Patel BP, Grima D. Cost-Effectiveness Analysis of Ofatumumab for the Treatment of Relapsing-Remitting Multiple Sclerosis in Canada. Pharmacoecon Open. 2022 Nov;6(6):859-870. doi: 10.1007/s41669-022-00363-1. Epub 2022 Sep 15. PMID: 36107307; PMCID: PMC9596641.

[vi] Treatment experience, burden, and unmet needs (TRIBUNE) in multiple sclerosis study: The costs and utilities of MS patients in Canada. (2018). Journal of Population Therapeutics and Clinical Pharmacology, 19(1).

[vii] 1Butzkueven H, Kalincik T, Patti F, et al. Long-term clinical outcomes in patients with multiple sclerosis who are initiating disease-modifying therapy with natalizumab compared with BRACETD first-line therapies. Therapeutic Advances in Neurological Disorders. 2024;17. doi:10.1177/17562864231221331

[viii] Morrow, S. A., Clift, F., Devonshire, V., Lapointe, E., Schneider, R., Stefanelli, M., & Vosoughi, R. (2022). Use of natalizumab in persons with multiple sclerosis: 2022 update. Multiple Sclerosis and Related Disorders, 65, 103995. https://doi.org/10.1016/j.msard.2022.103995

[ix] Brownlee W, Amin A, Ashton L, Herbert A. Real-world use of cladribine tablets (completion rates and treatment persistence) in patients with multiple sclerosis in England: The CLARENCE study. Mult Scler Relat Disord. 2023 Nov;79:104951. doi: 10.1016/j.msard.2023.104951. Epub 2023 Aug 21. PMID: 37639781.

MS Canada

July 25, 2024

Ms. Suzanne McGurn
President and Chief Executive Officer
CDA-AMC
865 Carling Ave., Suite 600
Ottawa, ON
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Email: [redacted]

Dear Ms. McGurn,

I am writing to you on behalf of MS Canada, an important and longstanding partner in Canada's drug and technology landscape, to share our concerns with the lack of clear reimbursement criteria contained in Canada's Drug Agency's report "Alemtuzumab, Cladribine, Fingolimod, and Natalizumab as First-Line Treatments in Adult Patients with Highly Active Relapsing MS."

As an organization that provides information, support, and advocacy to Canadians affected by MS, and funds research to find the causes and cure for the disease, we want to ensure Canadians living with MS, and their families, can participate fully in all aspects of life. This includes a focus on the unmet needs (referenced in the report) including the unmet treatment needs of Canadians with highly active relapsing MS.

The report references a group of experts, the Canadian MS Working Group, who consider high-efficacy treatments as first-line options for patients with high disease activity, aggressive disease presentation, or rapidly evolving symptoms at onset, to prevent early disability worsening. As stated in our comments on the draft report, the importance of the major guidelines by both the American Academy of Neurology (AAN) and the Canadian MS Working Group (CMSWG), in addition to the real-world evidence (RWE), are overshadowed, however, by randomized controlled trial (RTC) data, or perceived lack thereof, within the draft recommendation. Both the AAN and CMSWG guidelines are clear in their recommendations for initiating treatment with a high-efficacy DMT in people who present with high disease activity at the time of diagnosis.

In Canada, the treatment of MS is largely dictated by reimbursement practices that follow an escalation approach, which is also based on limited evidence.[i] Over the past two decades, there has been significant growth in our understanding of the pathophysiology of MS and as a result the development of innovative and highly effective therapeutic targets. Treatment approaches have not evolved to reflect these advancements in MS treatment and governments continue to use the escalation approach as the foundational framework around drug plan decision-making.

As noted, there is an increasing shift to treat people with highly active MS with high-efficacy DMTs as soon as possible to avoid unnecessary damage and irreversible disability caused by suboptimal management of disease activity. Integrally dependent on early and effective treatment of MS is its timely diagnosis. Delays in diagnosis and care of MS are not new within the Canadian healthcare system; however, the pandemic caused significant disruption to the access and availability of healthcare services. The impact of this disruption has created a backlog of healthcare services which will further delay the diagnosis and treatment of MS for some Canadians who may have highly active disease. By the time they have received a diagnosis and initiated a treatment under the current reimbursement policy that mandates an escalation approach to treatment, they will have lost a potentially critical therapeutic window to preserve brain health and function. For people living with MS, time is brain.

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Poor prognostic factors are well documented and can predict individuals with highly active disease so that optimal treatment can be identified. These prognostic factors, along with the major guidelines should be used to build the criteria for initiation of a high-efficacy DMT in adults with highly active MS. By not providing clear reimbursement criteria in this report, we further delay access which results in unnecessary damage and irreversible disability leading to increased health care costs. The cost of a mild to moderate relapse is $7,275 (CAD) and a severe relapse is estimated to cost $17,458.[ii] This does not account for loss of productivity costs and other indirect costs associated with increased and often irreversible disability. The cost of MS in Canada is more than 3.4 billion dollars per year and continues to rise.[iii] MS costs Canada $1.33 billion annually in indirect expenses relating to reduced productivity, according to the 2023 Deloitte Access Economics report. This includes reduced employment, absenteeism, presenteeism, premature mortality, and informal care. MS can significantly impact an individual's ability to participate in the workforce. Even among those who are employed, the disease can affect their productivity while at work, or their ability to attend work regularly. These impacts lead to real costs to the economy that are borne by the individual, their employers, and different levels of government.

We understand from some provincial drug programs that there will now be further delays in implementing this report and that the absence of recommendations in the conclusions of the report will now be addressed via CDA-AMC's FMEC (Formulary Management Expert Committee) process, to provide provinces with criteria for use.

Because the unmet treatment needs of this patient population are a priority, and due to the lack of recommendations, we ask the CDA-AMC and FMEC to focus efforts on taking the 1L report already completed and develop criteria for use as quickly as possible. Additionally, it will be imperative for FMEC to work with clinicians using the existing evidence in conjunction with patient groups to develop the criteria to ensure relevancy and expedited implementation.

To assist with this urgency, the Canadian Network of MS Clinics (CNMSC) has developed draft criteria for both natalizumab (Tysabri) and cladribine (Mavenclad) for this specific patient population. We would recommend that these be considered by FMEC in their discussions.

I look forward to hearing from you.

Sincerely,

Benjamin Davis
Senior Vice-President, Mission
MS Canada
[redacted]

cc:
Dr. Penny Smyth - [redacted]a
Judith Glennie, J.L. Glennie Consulting Inc. - [redacted]
Julie Kelndorfer, MS Canada - [redacted]

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[i] Casanova, B.; Quintanilla-Bordás, C.; Gascón, F. Escalation vs. Early Intense Therapy in Multiple Sclerosis. J. Pers. Med. 2022, 12, 119. https://doi.org/10.3390/jpm12010119

[ii] Baharnoori M, Bhan V, Clift F, Thomas K, Mouallif S, Adlard N, Cooney P, Blanchette F, Patel BP, Grima D. Cost-Effectiveness Analysis of Ofatumumab for the Treatment of Relapsing-Remitting Multiple Sclerosis in Canada. Pharmacoecon Open. 2022 Nov;6(6):859-870. doi: 10.1007/s41669-022-00363-1. Epub 2022 Sep 15. PMID: 36107307; PMCID: PMC9596641.

[iii] https://mscanada.ca/sites/default/files/documents/2023-10/deloitte-covid-19-impact-english_0.pdf

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Alemtuzumab, Cladribine, Fingolimod, and Natalizumab as First-Line Treatments in Adult Patients with Highly Active Relapsing MS

Project number: HT0038-000
Primary contact: Jennifer McDonell
Submitting organization: MS Canada

Is the information contained within the report complete? Are there any inconsistencies in the report, or is any relevant information missing?

A longstanding challenge in the pharmacoeconomic review of multiple sclerosis (MS) disease-modifying therapies for public payer decision-making is the lack of head-to-head comparison studies. The systematic review was thorough, though emphasized significant evidence gaps across a variety of outcomes as it relates to people living with highly active MS (HAMS).

In Canada, the treatment of MS is largely dictated by reimbursement practices that follow an escalation approach, which is also based on limited evidence.[i] Over the past two decades, there has been significant growth in our understanding of the pathophysiology of MS and as a result the development of innovative and highly effective therapeutic targets. Treatment approaches have not evolved to reflect these advancements in MS treatment and governments continue to use the escalation approach as the foundational framework around drug plan decision-making.

The importance of the major guidelines by both the American Academy of Neurology (AAN) and the Canadian MS Working Group (CMSWG), in addition to the RWE, are overshadowed by RTC data, or perceived lack thereof, within the draft recommendation. Both the AAN and CMSWG guidelines are clear in their recommendations for initiating treatment with a high-efficacy DMT in people who present with high disease activity at the time of diagnosis.

As noted, there is an increasing shift to treat people with highly active MS with high-efficacy DMTs as soon as possible to avoid unnecessary damage and irreversible disability caused by suboptimal management of disease activity. Integrally dependent on early and effective treatment of MS is its timely diagnosis. Delays in diagnosis and care of MS are not new within the Canadian healthcare system; however, the pandemic caused significant disruption to the access and availability of healthcare services. The impact of this disruption has created a backlog of healthcare services which will further delay the diagnosis and treatment of MS for some Canadians who may have highly active disease. By the time they have received a diagnosis and initiated a treatment under the current reimbursement policy that mandates an escalation approach to treatment, they will have lost a potentially critical therapeutic window to preserve brain health and function. For people living with MS, time is brain.

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Poor prognostic factors are well documented[ii] and can predict individuals with highly active disease so that optimal treatment can be identified. These prognostic factors, along with the major guidelines should be used to build the criteria for initiation of a high-efficacy DMT in adults with highly active MS who are treatment-naïve.

The current CADTH draft recommendation lacks clarity and direction on how jurisdictions will use this recommendation to move forward to improve the treatment approach for people living with highly active MS. We understand that CADTH is evolving to include RWE in HTAs; however, this recommendation does not reflect this as it focuses on the RTC data versus highlighting the major guidelines and RWE.

Are there any knowledge mobilization tools that you would like to see created based on this report?

Provide clear reimbursement criteria using the major guidelines and HAMS prognostic factors to assist governments in making the necessary updates to their benefits and coverage plans.

Increase the awareness and critical importance of early treatment and the concept of 'the right medication, at the right time', a concept that is not currently supported by Canadian drug plans.

The importance of shared decision-making between the person living with MS and their prescribing neurologist (and larger MS healthcare team) about their treatment plans.

Inform governments of the cost incurred for suboptimal treatment in addition to the cost of the DMT. The cost of a mild to moderate relapse is $7,275 (CAD) and a severe relapse is estimated to cost $17,458.[iii] This does not account for loss of productivity costs and other indirect costs associated with increased and often irreversible disability.

The cost of MS in Canada is more than 3.4 billion dollars per year and continues to rise.[iv] MS costs Canada $1.33 billion annually in indirect costs relating to reduced productivity, according to the 2023 Deloitte Access Economics report. This includes reduced employment, absenteeism, presenteeism, premature mortality, and informal care. MS can significantly impact an individual's ability to participate in the workforce. Even among those who are employed, the disease can affect their ability to attend work and their productivity while at work. These impacts lead to real costs to the economy that are borne by the individual, their employers, and different levels of government.

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

Canadians living with multiple sclerosis (MS) have a right to access all Health Canada-approved disease-modifying therapies (DMTs), including biosimilar and generic MS medications. Their patient voice is central to the goals of eliminating or reducing symptoms, slowing, preventing, and ultimately curing the disease. This requires timely, equitable, affordable, and consistent access to the full array of approved treatments, ranging from longstanding compounds to more recently approved innovative agents because no two people have the same disease course or respond in the same way to the same medication.

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A central premise must include the concept of "the right medication at the right time."

> This enables Canadians living with MS to benefit from those medications most appropriate for them regardless of where they live or their income status, and their patient voice is integral in this decision.
>
> Early intervention is vital to avoid many of the long-term health, economic, and personal costs that result from unnecessary irreversible disability.
>
> MS treatment decision-making should be made jointly between the person living with MS and their healthcare team.

Canadian drug programs must offer the full range of Health Canada-authorized medicines for MS. This includes different classes of medications and administrations as the clinical response to each of these drugs will vary greatly from person to person based on their unique patient journey including disease type and course, stage of life (pediatric, pregnancy, elderly), and personal preferences driven by lifestyle, health, and economic factors.

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[i] Casanova, B.; Quintanilla-Bordás, C.; Gascón, F. Escalation vs. Early Intense Therapy in Multiple Sclerosis. J. Pers. Med. 2022, 12, 119. https://doi.org/10.3390/jpm12010119

[ii] https://practicalneurology.com/articles/2022-feb/prognostic-factors-in-multiple-sclerosis/pdf

[iii] Baharnoori M, Bhan V, Clift F, Thomas K, Mouallif S, Adlard N, Cooney P, Blanchette F, Patel BP, Grima D. Cost-Effectiveness Analysis of Ofatumumab for the Treatment of Relapsing-Remitting Multiple Sclerosis in Canada. Pharmacoecon Open. 2022 Nov;6(6):859-870. doi: 10.1007/s41669-022-00363-1. Epub 2022 Sep 15. PMID: 36107307; PMCID: PMC9596641.

[iv] https://mscanada.ca/sites/default/files/documents/2023-10/deloitte-covid-19-impact-english_0.pdf

Multiple Sclerosis Society of Canada Feedback Submission

Proposed Project Scope DR0087-000

Alemtuzumab, cladribine, fingolimod, and natalizumab as first-line treatments in patients with highly active relapsing multiple sclerosis

February 2022

1. Do you think that the project as proposed in the project scope document will be useful to those making policy or clinical practice decisions? Why or why not?

A key strategic priority area for the MS Society is access to timely and effective treatments for people living with MS and we are very pleased to see that CADTH is considering the project *Alemtuzumab, cladribine, fingolimod, and natalizumab as first-line treatments in patients with highly active relapsing multiple sclerosis* as an area for further review and discussion.

Current drug policy in Canada rarely allows people living with MS to initiate treatment with a high efficacy therapy because of the associated strict and limiting reimbursement criteria. This criterion, shapes how clinicians are able to treat the disease, even in patients with a highly active disease course. The MS Society believes that Canadians living with MS have a right to access all Health Canada approved disease-modifying therapies (DMTs). In addition, their patient voice is central to the goal to eliminate or reduce symptoms, slow, prevent and ultimately cure the disease. This requires timely, equitable, affordable, and consistent access to the full array of approved treatments, ranging from longstanding compounds to more recently approved innovative agents, because no two-people have the same disease course or respond in the same way to the same medication.

A central premise must include the concept of "the right medication at the right time”

- this enables Canadians living with MS to benefit from those medications most appropriate for them regardless of where they live, their income status or treatment history, and their patient voice is integral in this decision.
- early intervention with the most appropriate medication is vital to avoid many of the long-term health, economic and personal costs that result from unnecessary irreversible disability.

Canadian drug programs must offer the full range of Health Canada authorized medicines for MS and be flexible to allow for different treatment approaches to be utilized based on clinical presentation and treatment goals as discussed between the clinician and patient. This includes different classes of medications and administrations as the clinical response to each of these drugs will vary greatly from person to person based on their unique patient journey including disease type and course, stage of life (pediatric, pregnancy, elderly), and personal choices driven by lifestyle, health, and economic factors. The MS Society believes that the proposed project will provide substantial evidence to support policy change, and provide MS clinicians, in collaboration with their patients, the opportunity to treat MS with the right medication, at the right time.

2. Are there policy, practice or research questions not considered in the project scope that are required to change or influence practice? If so, what would these be?

1. A research question related to patient reported outcomes and determinants of health is not addressed in the proposed project scope. Evidence-based drug access decisions require a determination of risk tolerance. Whether this is made on an individual or national basis, those impacted by the decision are in the best position of making this determination. That is, patients. Patients must be engaged as equal partners in all consultations that affect their care.

2. In most jurisdictions, reimbursement criteria dictate that patients must fail (demonstrate a lack of responsiveness or intolerance to) one or more low to moderate efficacy DMTs before they qualify for treatment with a high efficacy DMT. The concept of early intervention as a beneficial health outcome for patients with highly active MS is therefore lost, and often a significant amount of time passes before they initiate treatment with a high efficacy medication. This lost time in MS translates to unnecessary and sometimes permanent damage caused by treating the disease using a suboptimal approach.

Diagnostic criteria influence the reimbursement practices, however there is inconsistent use of the most up-to-date diagnostic criteria for MS across Canada. Many provinces and territories continue to apply criteria that was developed more than a decade ago. Since then, there have been significant advances in therapeutics for MS as well as updated diagnostic criteria, however, use of this outdated criteria, limits effective, and optimal treatment options for Canadians with highly active MS. Additional access concerns include the inequitable availability of Health Canada approved DMTs across Canada. Specific to the four drugs under review, only one, fingolimod, is consistently listed across all provincial, territorial, and federal formularies. Interestingly, fingolimod is also the only second-line agent available as a generic costing approximately 75 per cent less per unit than branded fingolimod. While the MS Society acknowledges CADTH's role is to provide evidence-based reports to governments to assist with decision making and is not responsible to implement policy change, we did want to highlight the current inequitable access to the medications proposed for review.

Repercussions of suboptimal treatment can result in greater financial burden to health and social systems. In Canada the average cost of a disease modifying therapy for multiple sclerosis is between approximately $7,000 and more than $50,000 per patient, per patient treatment year. Without access to early or effective treatment, individuals are at high risk of hospitalization due to acute disease exacerbations. In Canada, the average cost of disease worsening per year in an individual living with MS with mild disability was estimated at $30,836, moderate disability was estimated at $46,622 per year and severe disability at $77,981[i]. It is critical that CADTH considers the costs associated with burden of disease in relation to the overall cost of the DMTs, as well as patient choice of each of the DMTs under review including mode of administration, mechanism of action, and dosing schedules. Health outcomes need to be inclusive of the broader social determinants of health and not limited to drug budgets.

3. Do you have any suggestions for improving the project as proposed in the project scope document?

While CADTH has indicated that stakeholder feedback will take place at key stages of the project, there is a perceived lack of patient perspective embedded within the scope of the project itself. This could be improved with the inclusion of an individual with lived or living experience with MS to participate on the review panel to support this project. Finally, including patient reported outcome studies will provide a comprehensive analysis of the lived experience as part of the review.

4. Please provide any additional comments you may have about this document or the project itself, including any studies you think should be included in our review. (A list of included studies and the final project protocol will be posted at a later date.)

In summary, the MS Society is very pleased that CADTH has initiated the proposal of this project and for the opportunity to provide feedback regarding the project scope. Offering the full range of therapies that can reduce disease activity improves the chance of finding the best option for each person with MS so that personalized treatment can be optimized. This policy and practice change must be widely accepted and urgently adopted to give clinicians and patients a therapeutic strategy that offers the best chance of preserving brain and spinal cord tissue early in the disease course.

There is a growing body of evidence to support initiation of MS treatment with a high efficacy DMT versus an escalation approach in patients with MS. In addition to the studies the CADTH project team will identify through their systematic review, the MS Society is listing the following documents and patient reported outcome studies as part of the review.

Accessing Disease-Modifying Therapies for Multiple Sclerosis: A Pan-Canadian Analysis. (Conference Board of Canada)
Atlas of MS 3rd edition, Part 1: Mapping multiple sclerosis around the world – key epidemiology findings.
Brain health: time matters in multiple sclerosis
Treatment Optimization in Multiple Sclerosis: Canadian MS Working Group Recommendations[ii]
Multiple Sclerosis in the Workplace Supporting Successful Employment Experiences. (Conference Board of Canada)
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Contact:
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[redacted]

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[ii] Freedman, M., Devonshire, V., Duquette, P., Giacomini, P., Giuliani, F., Levin, M., . . . Yeh, E. (2020). Treatment Optimization in Multiple Sclerosis: Canadian MS Working Group Recommendations. Canadian Journal of Neurological Sciences / Journal Canadien Des Sciences Neurologiques, 47(4), 437-455. doi:10.1017/cjn.2020.66

CDA-AMC Open Calls for Input and Feedback

Proposed Project Scope for "Cladribine and Natalizumab for Highly Active Relapsing-Remitting Multiple Sclerosis"

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

Brand Name: Mavenclad and Tysabri

Generic Name: Cladribine and Natalizumab

Indication(s): Highly Active Relapsing-Remitting Multiple Sclerosis

Group Name: Canadian Network of MS Clinics (CNMSC)

Primary contact: Dr. Sarah Morrow

E-mail: [redacted]

Telephone: [redacted]

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 transitions the May 2024 "first-line (1L) review" (i.e., evaluation of the role of alemtuzumab, cladribine, fingolimod, natalizumab, and rituximab as 1L treatments in adults living with highly active relapsing MS[2]) to the FMEC process with a focus on cladribine and natalizumab. It is imperative that the outputs of this process are finalized and implemented as quickly as possible, to provide access to these medications and mitigate the serious negative impact/permanent disability of this highly active form of MS.

CNMSC previously provided insights and feedback to the initial call for input (February 16, 2022), a response to the call for input regarding studies included in review (October 31, 2023), and a response to the draft report (March 20, 2024). These submissions are provided again as attachments, for ease of reference for CDA-AMC staff. Our August 6,2024 comments to CDA-AMC and provincial payers – which included proposed criteria – are also included with this submission.

We would also like to provide the following advice to FMEC as they approach this review:

- It is important for FMEC to consider that jurisdictions requested the evaluation of these products and are looking to make an informed policy decision on how to make these products available for patients based on the full scope of evidence available.
    - Of note, some provinces were already funding these products on a case-by-case basis prior to the launch of the 1L review (e.g., Ontario). Quebec also funds Tysabri for this

[1] CNMSC is a national network of academic and community-based clinics established for the advancement of patient services, education, and research in MS.
[2] CDA-AMC. Alemtuzumab, Cladribine, Fingolimod, and Natalizumab as First-Line Treatments in Adult Patients With Highly Active Relapsing Multiple Sclerosis (May 30, 2024). https://www.cadth.ca/alemtuzumab-cladribine-fingolimod-and-natalizumab-first-line-treatments-adult-patients-highly

patient population; thus, equitable access is also an important consideration for the committee.

- Given that much of the key evidence supporting the role of cladribine and natalizumab in highly-active MS is based in robust real-world evidence (RWE), CNMSC believes that it is important for CDA-AMC to pull in RWE expertise from within and/or outside of the organization to help with the interpretation of this evidence and its application in decision-making.
    - The highly active MS population is limited, such that the ability to carry out RCTs has been constrained. The RWE data available addresses the important questions of effectiveness of these agents in this population.
- Ultimately, we believe that FMEC should be able to conclude that, based on the evidence available, that the data are sufficiently robust to support funding of these products in a select group of patients via case-by-case review processes based on specific criteria for use.

Specific comments on the project scope

a) General comments:

The following outlines comments from CNMSC on more general components of the proposed project scope.

Parameter	CDA-AMC proposal	CNMSC comments
Objectives	The objective of this review is to assess the comparative efficacy and harms of cladribine and natalizumab for the first-line treatment of highly active RRMS.	• CNMSC believes that the objective should also include a commitment to developing practical criteria for use by the jurisdictions, based on the outcomes of the review. • CNMSC is concerned that FMEC will start the evidence evaluation process all over again, something that has already taken well over 2 years to complete. • FMEC should focus its efforts on taking the 1L report already completed and developing criteria for use as quickly as possible.
Policy Question	Should cladribine and natalizumab be reimbursed as first-line therapies in adult patients with highly active RRMS?	CNMSC has no additional comments regarding the policy question.
Economic analysis	A cost comparison table will be developed using list prices from a public drug plan incorporating the dosing regimens as described within the respective Product Monographs.	CNMSC recommends summarizing costs over 2 time frames: a) yearly costs; and, b) a 3 to 5-year time period, in order to enable more accurately compare costs associated with different regimens.

b) Research questions

The following table outlines the research questions that CDA-AMC have proposed for this project. CNMSC believes that there are important clarifications needed to these questions, as outlined below.

Research question	CNMSC comments
1. What is the clinical efficacy and safety of natalizumab and cladribine as first-line treatments in patients with highly active relapsing-remitting multiple sclerosis compared to drugs currently used as first-line treatment in adult patients with highly active RRMS?	• CNMSC does not believe that the research question proposed is relevant. • The relevant question for policy makers is whether there is sufficient evidence of effectiveness for natalizumab and cladribine in the 1L setting for patients with highly active MS. • Another factor that needs to be considered as part of the research question is the harm of NOT starting high-efficacy treatments in patients with highly active disease, given the clinical/disability and economic implications of delayed therapy. References related to this

	issue are captured in the Canadian Treatment Optimization Recommendations (see citation below). • As noted in the PICOs evaluation below, none of the available disease modifying agents is specifically indicated as a 1L agent in highly active MS. • Also, see below re: definition of highly active disease.
2. How do costs compare across disease modifying therapies for the treatment of adult patients with highly active RRMS?	• This question needs to be clarified further, to the following: "How do costs compare for those DMTs that have demonstrated effectiveness in the treatment of adult patients with highly active MS?" • As noted above, CNMSC recommends summarizing costs over 2 time frames: a) yearly costs; and, b) a 3 to 5-year time period, in order to enable more accurately compare costs associated with different regimens.

c) Additional areas for clarification

i) Definition of highly active disease

- It is important that CDA-AMC addresses what appears to be confusion in the project scope regarding the difference between what is referred to as "active disease/MS" vs. the definition of "highly active disease/MS". This impacts the scope of data to address the policy question of whether or not cladribine and/or natalizumab should be funded for patients with highly active MS.
- We hope that the following provides clarity of the differences between these two descriptors.

- "Active MS"
    - Patients who have a flair or relapse of their MS (i.e., based on MRI findings and/or clinical signs and symptoms of MS) at a point in time are considered to have "active" disease, or new lesions on their routine MRI
- "Highly active MS"
    - Patients with highly active disease are a specific subset of patients whose MS is very active clinically (several relapses or relapses without recovery or several new clinically silent MRI lesions or those with spinal cord lesions) and, thus, at risk of creating significant disability over a short time period (see Table 1 below).
    - CNMSC provided a clear definition for highly active MS[3] in its February 2022 submission, as well as an explanation for the absence of stratification for this population in its October 2023 submission (i.e., the "highly active disease" terminology is relatively recent and, as a result, it has not traditionally been used as a selection criterion to design specific trials in this population).
        - Examination of individuals with highly active disease *a priori* was not a consideration at the time of most of the original studies, as the science had not evolved sufficiently to identify this as a relevant subgroup that should be carved out for specific/differential examination.
    - The Canadian Treatment Optimization Recommendations (TOR)[4] speak to the identification and treatment of aggressive forms of the disease, an area of emphasis because of the critical importance of achieving disease control in these patients.
        - Patients with highly active disease are at significant risk of early disability worsening and warrant early treatment with a higher-efficacy DMT.
        - Patients at risk of a more aggressive clinical course, worse outcomes, and/or a poorer response to DMTs include males, individuals of non-white ethnicity, and those with high-risk clinical/radiological disease factors.

[3] Rush, C. A. et al. Aggressive multiple sclerosis: proposed definition and treatment algorithm. Nat. Rev. Neurol. 11, 379–389 (2015); published online 2 June 2015; doi:10.1038/nrneurol.2015.85

[4] Freedman M et al. (2020). Treatment Optimization in Multiple Sclerosis: Canadian MS Working Group Recommendations. Canadian Journal of Neurological Sciences, 1-19. doi:10.1017/cjn.2020.66he

- Evidence of highly active disease (e.g. frequent relapses, new MRI lesions), extensive CNS involvement (multifocal, lesion number and location, T2 burden of disease) and/or inadequate recovery/repair (residual impairment, higher baseline EDSS score) or cognitive reserve are prognostic of a worse clinical course and poorer long-term outcomes in CIS and RMS.

Table 1. Defining highly active MS.

Defining 'aggressive' MS:

- Rampant progression of disability over a short time period
- Early, unexpected acquisition of disability followed by frequent relapses (often with incomplete resolution) and highly active disease seen on MRI
- As any type of MS that is associated with repeated severe attacks and accelerated accrual of disability
- We suggest that aggressive MS can be defined as RRMS with **one or more** of the following features:
  - EDSS score of 4 within 5 years of onset
  - Multiple (two or more) relapses with incomplete resolution in the past year
  - More than two MRI studies showing new or enlarging T2 lesions or gadolinium-enhancing lesions despite treatment
  - No response to therapy with one or more DMTs for up to 1 year

Early identification:

- Important to identify patients who are at risk of aggressive MS as early as possible and implement an effective treatment strategy
- Early intervention might protect patients from irreversible damage and disability, and prevent the development of a secondary progressive course
- Population studies have indicated that relapses occurring in the first 2 years of MS drive early disease progression, with diminishing contribution from later relapses (after year 3).

Approach to management:

- The window of opportunity for treating patients with aggressive MS is narrow, thus, conventional treatment paradigms need to be reconsidered.
- Evidence over the past decade points to a window of opportunity for effective treatment in patients with MS, which covers the period of peak CNS inflammation.
- Current DMTs target the early type of CNS inflammation that is believed to substantially contribute to demyelination and axonal damage. Therefore, these therapies are more effective when the inflammatory process is prevalent, as in the early stages of disease.
- Early disability progression seems to be driven by inflammation, but later progression is associated with an ill-defined chronic neurodegenerative process, which is mostly unamenable to treatment with currently available therapies.
- The goal of treatment is to minimize the accumulation of irreversible disability and, ultimately, to slow or stop disease progression, thus minimizing long-term disability and preserving a good quality of life.
- Therefore, conventional treatment paradigms need to be reconsidered in patients with aggressive MS, so as to avoid late identification and subsequent treatment with aggressive treatments that offer too little too late.

d) Systematic review selection criteria

The following table outlines the PICOs that CDA-AMC has proposed for this project. CNMSC believes that there are important clarifications and/or changes needed to these parameters, as outlined below.

Criteria	Description	CNMSC comments
Population	DMT-naïve adults with highly active relapsing MS Potential Subgroups • age at diagnosis (e.g., 18 years to < 50 years; ≥ _50 years) • Time since diagnosis (to account for disease duration) • EDSS score (e.g., < 3; 3 to < 6; ≥ 6) • MRI activity at baseline	No additional comments.
Interventions	Cladribine 3.5mg/kg orally over 2 years, administered as 1 treatment course of 1.75mg/kg per year Natalizumab 300mg IV infusion every 4 weeks	• It should be noted that long-term data have demonstrated the long-term durability of the time-limited treatment course for cladribine. This should be taken into consideration in the comparative costing of regimens (see comment above re: economic analysis)
Comparators	Relapsing MS first-line therapies:[a] • Interferons (interferon beta-1A, interferon beta-1B)	• Interferons, glatiramer, dimethyl fumarate, and terifunomide would NOT be considered as

	• Glatiramer acetate • Dimethyl fumarate • Teriflunomide • Ocrelizumab • Ofatumumab	appropriate agents for use in a patient with highly active disease. • It is because these agents are not useful in these patients that clinicians have been engaging with payers across the country since 2020 to get access to cladribine and natalizumab for this specific subpopulation of patients. • See above re: difference between "active" disease vs. "highly active" disease.
Outcomes	**Efficacy:** • Relapses (e.g., relapse rate, relapse-free rate, time to relapse) • Disability progression (including time to progression) or improvement • Function (e.g., MSFC score including T25-FW, or 9-HPT individual scores) • Imaging outcomes (e.g., MRI brain lesions, MRI brain volume, spinal cord imaging) • Cognitive outcomes (e.g., MSNQ, PASAT 3, SDMT) • Symptoms (e.g., Fatigue, cognition, mobility, visual disturbance) • HRQoL (e.g., MSQOL-54, MSQLI, MS-QLQ27) • Instrumental activities of daily living (e.g., absenteeism, presentism, employment status) **Safety:** • Adverse events • Serious adverse events • Withdrawal due to adverse events • Mortality • Notable harms: injection-related reactions, opportunistic infections, serious infections, progressive multifocal leukoencephalopathy, lymphopenia, neutropenia, malignancies	No additional comments.
Study design	Published phase II, phase III and phase IV RCTs If no RCTs are available to adequately inform the research question: comparative prospective cohort studies	CDA-AMC needs to commit to a fulsome evaluation of the RWE available reflecting the use of cladribine and/or natalizumab in highly active MS. The May 2024 review systematically excluded this information, despite the fact that the data for this specific subgroup of patients consistently demonstrates a positive clinical benefit in the real-world setting.
Search dates	TBD	

9-HPT = 9 Hole Peg Test; DMT = disease-modifying therapies; EDSS = Expanded Disability Status Scale; HRQoL = health-related quality of life; MS = multiple sclerosis; MSFC = multiple sclerosis functional composite; MSNQ = multiple sclerosis neuropsychological questionnaire; MSQLI = multiple sclerosis quality of life inventory; MSQLQ27 = 27-item multiple sclerosis quality of life questionnaire; MSQOL-57 = multiple sclerosis quality of life-54; PASAT 3 = 3-second Paced Auditory Serial Addition Task; RCT = randomized controlled trial; SDMT = symbol digit modality test; T25-FW = Timed 25-foot walk.

[a] Health Canada-recommended dosage for MS or clinically relevant dosage based on expert advice or on the Canadian MS Working Group guidelines.

e) References

The list of references cited by CDA-AMC in its proposal is highly limited in scope. It is assumed that a more fulsome search will be undertaken to identify the full body of evidence available to address the policy questions at hand.

Previous CNMSC submissions have provided citations and reference summaries relevant to this project. CNMSC is submitting those submissions again, to ensure there is no duplication of effort.

Additional references that CDA-AMC should consider as part if its review include the following:

- Oh J, Bhan V, Traboulsee A, et al. Health Canada Drug Approval Process: A Barrier to Personalized Care in Multiple Sclerosis. Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques. Published online 2024:1-4. doi:10.1017/cjn.2024.267

August 6, 2024

Ms. Suzanne McGurn
President and Chief Executive Officer
CDA-AMC
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Email: [redacted]

Dear Ms. McGurn

As you may be aware, 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.

We are contacting you today regarding the status of and continued delays to the CDA-AMC review regarding the role of alemtuzumab, cladribine, fingolimod, natalizumab, and rituximab as first-line (1L) treatments in adults living with highly active relapsing MS.[2]

More precisely, we encourage CDA-AMC to move forward with finalizing the information needed by provincial drug plans to implement the results of this review as soon as possible, so that patients may benefit from these therapies.

Background:

CNMSC has put a great deal of effort into providing insights and feedback since the launch of the review of these four products in February 2022. Specifically, CNMSC provided a response to the initial call for input (February 16, 2022), a response to the call for input regarding studies included in review (October 31, 2023), and a response to the draft report (March 20, 2024). (We are pleased to provide copies of these documents to you and/or provincial drug program leads for your files, on request.)

CNMSC was pleased to see CDA-AMC acknowledge that the optimal management of MS has evolved significantly. As noted in the final version of the review, it is critical to have timely access to 1L higher efficacy options for select patients with aggressive disease to avoid the rapid disability accumulation associated with this variant of MS. We know that achieving disease control as quickly as possible results in mitigation of disability and/or worsening disease in the long-term. This ultimately benefits health outcomes in persons living with MS (PLWMS), as well as direct (i.e., health system) and indirect (i.e., productivity, social assistance) costs.

On the other hand, as noted in our March 2024 submission, the recommendations in the 1L report should have been more precise in terms of defining criteria for leveraging these products in highly active MS. In addition, the review should have put more emphasis on and incorporated a more detailed summary of the available real-world evidence, as those results are compelling and highly relevant to the policy question at hand.

CNMSC provided suggested criteria for use in both its February 2022 and October 2023 submissions, based on the full body of available evidence as well as the 2020 Canadian Treatment Optimization

[1] CNMSC is a national network of academic and community-based clinics established for the advancement of patient services, education, and research in MS.
[2] CDA-AMC. Alemtuzumab, Cladribine, Fingolimod, and Natalizumab as First-Line Treatments in Adult Patients With Highly Active Relapsing Multiple Sclerosis (May 30, 2024). https://www.cadth.ca/alemtuzumab-cladribine-fingolimod-and-natalizumab-first-line-treatments-adult-patients-highly

Recommendations referenced in the CDA-AMC report.

Current Status:

Based on recent discussions with some provincial drug programs, we understand that there will now be further delays to implementing this report. Apparently, the absence of specific direction for operationalizing the report will now be addressed via CDA-AMC's FMEC (Formulary Management Expert Committee) process, with the goal of providing participating drug plans with criteria for use. There does not appear to be a specific timeline available for this initiative.

Our greatest concern is that FMEC will start the evidence evaluation process all over again, something that has already taken well over 2 years to complete. During this time, patients with aggressive disease have experienced delays in accessing highly efficacious treatments. With this latest development, we only see the delays continuing – to the detriment of patients. Getting access to these products to enable timely treatment was the whole reason that MS clinicians in Ontario started this initiative back in June 2020.

We implore CDA-AMC and FMEC to focus efforts on taking the 1L report already completed and developing criteria for use as quickly as possible. We also ask that FMEC work with clinicians with expertise in MS to develop these criteria to ensure they are both relevant and practical to implement.

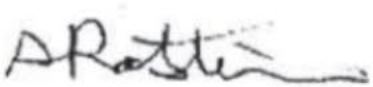
Based on discussions with various jurisdictions, CNMSC has developed draft criteria for both natalizumab (Tysabri) and cladribine (Mavenclad) for this specific patient population (see Appendix I).
We recommend that these be considered by FMEC in their deliberations. CNMSC members would also welcome the opportunity to work with FMEC to refine and/or develop additional criteria as needed.

Conclusions:

It is imperative that CDA-AMC, the FMEC process, and provincial drug programs ensure that the recommendations of the 1L report are implemented as quickly as possible, to provide access to these medications and mitigate the serious negative impact/permanent disability of this highly active form of MS. As an organization, we remain committed to supporting CDA-AMC in their efforts. We strongly encourage FMEC to reach out to CNMSC and include clinicians with specific expertise in MS in their process to ensure that the criteria developed are relevant and pragmatic.

Please do not hesitate to reach out to us.

Best regards,



Dr. Dalia Rotstein, on behalf of CNMSC
Neurologist - St. Michael's Hospital
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October 31, 2023

CADTH
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Ottawa, ON Canada K1S 5S8

To whom it may concern:

I am writing to you on behalf of the Canadian Network of Multiple Sclerosis Clinics (CNMSC; https://cnmsc.ca/), which is a national network of academic and community-based clinics established for the advancement of patient services, education, and research in MS. As you are aware, CNMSC members provided comprehensive input to CADTH's review of specific first-line (1L) therapies in February 2022.

The purpose of this communication is to provide feedback to CADTH on the "List of included studies"[1] for project HT0038 Drugs for aggressive RRMS.[2] We have concerns on two specific fronts – the scope of evidence and the importance of having a thorough understanding of the disease process.

The studies proposed for inclusion in this evidence review are very limited in scope, which appears to be related to a fundamental flaw in CADTH's search terms (i.e., focus on terms such as "aggressive" MS). As a result, the studies proposed fall far short of the scope of evidence available to describe the value of these agents in patients with highly-active MS. We are also concerned that there is a gap in understanding of the disease process and, therefore, appropriate context on the part of CADTH staff as it relates to the definition of MS patients with highly-active disease. We address both of these issues as part of our input below.

a) Definitions

In its February 2022 submission to CADTH, CNMSC provided a definition for "aggressive MS" (i.e., highly-active disease/MS)[3] as well as articulating the rationale for/importance of proactive treatment of patients presenting with this subtype of MS. This information is re-capped in Table 1 below, for ease of reference.

The Canadian Treatment Optimization Recommendations (TOR)[4] speak to the identification and treatment of aggressive forms of the disease, an area of emphasis because of the critical importance of achieving disease control in these patients.

- Patients with highly-aggressive disease are at significant risk of early disability worsening and warrant early treatment with a higher-efficacy DMT.
- Patients at risk of a more aggressive clinical course, worse outcomes, and/or a poorer response to DMTs include males, individuals of non-white ethnicity, and those with high-risk clinical/radiological disease factors.
- Evidence of highly active disease (e.g. frequent relapses, new MRI lesions), extensive CNS involvement (multifocal, lesion number and location, T2 burden of disease) and/or inadequate recovery/repair (residual impairment, higher baseline EDSS score) or cognitive reserve are prognostic of a worse clinical course and poorer long-term outcomes in CIS and RMS.

[1] CADTH. List of included studies. https://www.cadth.ca/sites/default/files/hta-he/HT0038%20MS%20List%20of%20included%20studies_refchecked.pdf
[2] CADTH. Health Technology Review - Alemtuzumab, Cladribine, Fingolimod, and Natalizumab as First-Line Treatments in Adult Patients With Highly Active Relapsing Multiple Sclerosis. https://www.cadth.ca/alemtuzumab-cladribine-fingolimod-and-natalizumab-first-line-treatments-adult-patients-highly
[3] Rush, C. A. et al. Aggressive multiple sclerosis: proposed definition and treatment algorithm. Nat. Rev. Neurol. 11, 379–389 (2015); published online 2 June 2015; doi:10.1038/nrneurol.2015.85
[4] Freedman M et al. (2020). Treatment Optimization in Multiple Sclerosis: Canadian MS Working Group Recommendations. Canadian Journal of Neurological Sciences, 1-19. doi:10.1017/cjn.2020.66he

Table 1. Defining aggressive/highly active MS.

Defining 'aggressive' MS:
- Rampant progression of disability over a short time period
- Early, unexpected acquisition of disability followed by frequent relapses (often with incomplete resolution) and highly active disease seen on MRI
- As any type of MS that is associated with repeated severe attacks and accelerated accrual of disability
- We suggest that aggressive MS can be defined as RRMS with **one or more** of the following features:
  - EDSS score of 4 within 5 years of onset
  - Multiple (two or more) relapses with incomplete resolution in the past year
  - More than two MRI studies showing new or enlarging T2 lesions or gadolinium-enhancing lesions despite treatment
  - No response to therapy with one or more DMTs for up to 1 year

Early identification:
- Important to identify patients who are at risk of aggressive MS as early as possible and implement an effective treatment strategy
- Early intervention might protect patients from irreversible damage and disability, and prevent the development of a secondary progressive course
- Population studies have indicated that relapses occurring in the first 2 years of MS drive early disease progression, with diminishing contribution from later relapses (after year 3).

Approach to management:
- The window of opportunity for treating patients with aggressive MS is narrow, thus, conventional treatment paradigms need to be reconsidered.
- Evidence over the past decade points to a window of opportunity for effective treatment in patients with MS, which covers the period of peak CNS inflammation.
- Current DMTs target the early type of CNS inflammation that is believed to substantially contribute to demyelination and axonal damage. Therefore, these therapies are more effective when the inflammatory process is prevalent, as in the early stages of disease.
- Early disability progression seems to be driven by inflammation, but later progression is associated with an ill-defined chronic neurodegenerative process, which is mostly unamenable to treatment with currently available therapies.
- The goal of treatment is to minimize the accumulation of irreversible disability and, ultimately, to slow or stop disease progression, thus minimizing long-term disability and preserving a good quality of life.
- Therefore, conventional treatment paradigms need to be reconsidered in patients with aggressive MS, so as to avoid late identification and subsequent treatment with aggressive treatments that offer too little too late.

From a practical perspective, we recommend the following approach to patient identification and criteria for use of specific medications:

i) Patient identification
- From a demographic perspective, patients at risk of a more aggressive clinical course, worse outcomes, and/or a poorer response to DMTs include males, individuals of non-white ethnicity, and those with high-risk clinical/radiological or biomarker disease factors.
- From a clinical perspective, the following are some of the major signs and symptoms that are reflective of more aggressive disease and are prognostic of a worse clinical course and poorer long-term outcomes in CIS and RMS.
  - Evidence of highly active disease (e.g. frequent relapses, high burden of disease on MRI at onset, or new MRI lesions in a short time period);
  - Extensive CNS involvement (clinical evidence of widespread disease along with multifocal, lesion number and location, T2 burden of disease on MRI);
  - Inadequate recovery/repair (residual impairment, higher baseline EDSS score) post-relapse; and/or,
  - Early cognitive involvement.

ii) Criteria for use
- The following are suggested specific criteria for use for specific products.

- Mavenclad - suggested criteria for use:
  - For use in patients who are and have multiple poor prognostic factors
    - high burden on diagnostic MRI at baseline

        - AND
        - severe first relapse
        - OR
        - poor recovery from first relapse
    - For use in patients with active disease who want to get pregnant
    - Patient is being managed by an experienced MS expert working in an CNMSC-affiliated MS clinic

- Tysabri - suggested criteria for use:
    - For use in patients who are and have multiple poor prognostic factors
        - high burden on diagnostic MRI at baseline
        - AND
        - severe first relapse
        - OR
        - poor recovery from first relapse
    - Patient is being managed by an experienced MS expert working in an CNMSC-affiliated MS clinic

- Lemtrada - suggested criteria for use:
    - For use in patients who are and have multiple poor prognostic factors
        - high burden on diagnostic MRI at baseline
        - AND
        - severe first relapse
        - OR
        - poor recovery from first relapse
    - For use in patients with active disease who want to get pregnant
    - Patient is being managed by an experienced MS expert working in an CNMSC-affiliated MS clinic

b) Relevant studies

There are two issues to consider when determining what studies are relevant to answering the question of whether the products incorporated into this review have value in managing patients with highly-active MS. First is the timing of the studies in the context of the history of MS drug development and understanding that, at the time of the trials, placebo-controlled comparisons are valuable in addressing the question at hand. The second issue relates to CADTH's search terms, and the expectation of specific clinical trials focused solely on the "aggressive/highly active" MS population.

The following points articulate CNMSC's concerns with CADTH's approach and outline the studies that CNMSC believes should be included in the scope of this project.

- CADTH has made the assumption that doing a literature search using the search terms "aggressive/highly-active MS" will reveal the full evidence base to address the key question for this review.
    - This assumption is fundamentally flawed as this terminology is relatively recent and, as a result, it has not traditionally been used as a "selection criterion" to design specific trials in this population.
- Historically, there were many patients with highly-active MS enrolled in clinical trials, given the very limited treatment options available at the historical various times of pivotal trials.
    - It should be noted that designation of "highly-active" MS was not part of the diagnostic paradigm at the time.
- As a result, clinical trial results for many products include and, therefore reflect the impact of these products on this patient population.
    - For instance, the original phase 3 RCTs for natalizumab (and the other DMTs) should have been within scope for this project, as they were all first-line studies and included this patient population.

- CADTH has excluded trials that did not have an active comparator (i.e., placebo-controlled studies were excluded) and has missed some key comparative studies.
    - This disadvantages products such as natalizumab as it was studied at a time when few other therapies were available.
    - CADTH has also failed to include the natalizumab versus natalizumab + interferon study.

Given these issues CNMSC recommends that, in addition to the studies outlined by CADTH, the studies outlined in Table 2 should also be included in the review.

Table 2. Studies for inclusion in project HT0038

Study	Comments
Alemtuzumab	
Cohen JA et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial (CARE-I). Lancet 2012; 380: 1819–28. http://dx.doi.org/10.1016/S0140-6736(12)61769-3	First line
Hardova E et al. Alemtuzumab CARE-MS I 5-year follow-up: Durable efficacy in the absence of continuous MS therapy. Neurology 2017;89:1107–1116	First line extension trial
Fox EJ et al. Alemtuzumab improves neurological functional systems in treatment-naive relapsing-remitting multiple sclerosis patients. Journal of the Neurological Sciences 363 (2016) 188–194.	First line Alemtuzumab demonstrated a broad treatment effect in improving preexisting disability. These findings may influence treatment decisions in patients with early, active relapsing-remitting MS displaying neurological deficits.
Coles AJ et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial (CARE-II). Lancet 2012; 380(9856):1829-39. http://dx.doi.org/10.1016/S0140-6736(12)61768-1	Second line
CARE-MS I - Krieger S, Lubetzki C, Palmer J, Margolin DH. Alemtuzumab reduces disease activity in treatment-naive patients with highly active relapsing-remitting multiple sclerosis. Mult Scler J. 2014;Vol.20(1 suppl):106-107.	Included in CADTH list
Cladribine	
CLARITY - Giovannoni G et al. A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis (CLARITY). NEJM January 20, 2010. 10.1056/NEJMoa0902533	Original study A subset of the CLARITY study (said to have highly-active disease) showed even greater efficacy compared with overall study population.
CLARITY - Vermersch P, Galazka A, Dangond F, et al. Efficacy of cladribine tablets in high disease activity patients with relapsing multiple sclerosis: post hoc analysis of subgroups with and without prior disease-modifying drug treatment. Curr Med Res Opin. 2021;37(3):459-464.	Included in CADTH list Cladribine vs. placebo Subgroup analysis
ORACLE MS - Leist TP et al. Effect of oral cladribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE MS): a phase 3 randomised trial. Lancet Neurol 2014; 13: 257–67 http://dx.doi.org/10.1016/S1474-4422(14)70005-5	Evaluated the effect of oral cladribine on conversion to clinically definite MS in patients with a first clinical demyelinating event (i.e., use of cladribine in CIS) Attests to its use as a 1st line therapy and the importance of early treatment.
Freedman MS et al. The efficacy of cladribine tablets in CIS patients retrospectively assigned the diagnosis of MS using modern criteria: Results from the ORACLE-MS study. Multiple Sclerosis Journal - Experimental, Translational and Clinical. October-December 2017: 1-14. DOI: 10.1177/ 2055217317732802	Regardless of the criteria used to define CIS or MS, 3.5 mg/kg cladribine is effective in patients with a first clinical demyelinating attack
Fingolomod	
TRANSFORMS - Cohen JA, Barkhof F, Comi G, et al. Fingolimod versus intramuscular interferon in patient subgroups from TRANSFORMS. J Neurol. 2013;260(8):2023-3.	Included in CADTH list
FREEDOMS - Radue E-W, O'Connor P, Polman CH, et al. Impact of fingolimod therapy on magnetic resonance imaging outcomes in patients with multiple sclerosis. Arch Neurol. 2012;69(10):1259-69	Included in CADTH list
Devonshire V, Havrdova E, Rague E-W, et al. Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomised, placebo-controlled FREEDOMS study. Lancet Neurol. 2012;11(5):420-8	Included in CADTH list
Natalizumab	

Study	Comments
AFFIRM - Polman CH, O'Connor PW, Havrdová E, Hutchinson M, Kappos L, Miller DH, Phillips JT, Lublin FD, Giovannoni G, Wajgt A, Toal M, Lynn F, Panzara MA, Sandrock AW, AFFIRM Investigators (2006) A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 354(9):899–910	Patients 18-50yo diagnosed with relapsing MS with no previous treatment. Natalizumab reduced the risk of the sustained progression of disability and the rate of clinical relapse in patients with relapsing MS.
SENTINEL - Ernst-Wilhelm Radue, William H. Stuart, Peter A. Calabresi, Christian Confavreux, Steven L. Galetta, Richard A. Rudick, Fred D. Lublin, Bianca Weinstock-Guttman, Daniel R. Wynn, Elizabeth Fisher, Athina Papadopoulou, Frances Lynn, Michael A. Panzara, Alfred W. Sandrock. Natalizumab plus interferon beta-1a reduces lesion formation in relapsing multiple sclerosis, Journal of the Neurological Sciences Volume 292, Issues 1–2, 2010, Pages 28-35. https://doi.org/10.1016/j.jns.2010.02.012	
Hutchinson, M., Kappos, L., Calabresi, P.A. et al. The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analyses of AFFIRM and SENTINEL. J Neurol 256, 405–415 (2009). https://doi.org/10.1007/s00415-009-0093-1	"These results indicate that natalizumab is effective in reducing disability progres- sion and relapses in patients with relapsing MS, particularly in patients with highly active disease."
Wiendl H et al. Epoch Analysis of On-Treatment Disability Progression Events over Time in the Tysabri Observational Program (TOP). PLoS ONE 11(1): e0144834. doi:10.1371/journal.pone.0144834 Published: Jan 15/16	Disability progression rate decreased further beyond 2y of natalizumab treatment. Patients who responded well and remained on continuous natalizumab therapy for over 4 years had sustained and potentially enhanced reductions in EDSS progression over time.
Other references	
Brown et al. Association of Initial Disease-Modifying Therapy with Later Conversion to Secondary Progressive Multiple Sclerosis. JAMA. 2019;321(2):175-187. doi:10.1001/jama.2018.20588	Shows that initial treatment with fingo, nata or alemtuzumab delayed transition to SPMS compared to GA or IFNbeta
Kalincik et al. Comparative Effectiveness of Autologous Hematopoietic Stem Cell Transplant vs Fingolimod, Natalizumab, and Ocrelizumab in Highly Active Relapsing-Remitting Multiple Sclerosis. JAMA. 2023;80(7):702-713.	Compared effectiveness of AHSCT vs fingolimod, natalizumab, and ocrelizumab through a comparative treatment effectiveness study amongst 6 MS centres and international MSBase registry between 2006 to 2021. AHSCT was superior to fingolimod and marginally superior to natalizumab in preventing relapses and facilitating recovery from disability. There was no evidence for difference in effectivenesss of AHSCT and ocrelizumab.

c) Other considerations

Given the unique nature of this subpopulation of MS patients, it is important to look beyond traditional Phase III clinical trial data to gain an understanding of what MS medications have an impact on patients with highly-active MS. For instance, there is a body of data, particularly from Scandinavia, which articulates the role of rituximab as a first line option in MS. Given CADTH's recent emphasis on real-world evidence, there should be an effort to include this kind of information as part of the review process.

Summary

We welcome the opportunity to provide input into this project, as we know firsthand how critical it is to have higher efficacy options readily available 1L for select patients with aggressive disease to avoid serious disability associated with this form of MS. Timely completion of this report is critical for PLWMS and their long-term outcomes as, in our experience, provincial access to these medications will not move forward until this project is complete.

We hope that this input helps to accelerate completion of this project. In the meantime, we will continue to engage in CADTH's activities and invite you to reach out to me or any of our members if you need support in your efforts.

Best regards,

[redacted]

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Appendix I – Suggested criteria for use for 1L cladribine and natalizumab in highly active MS

Cladribine (Mavenclad)

Suggested criteria for use:

- For use in patients who are and have multiple poor prognostic factors, such as:
  - high burden on diagnostic MRI at baseline

  AND
  - severe first relapse

  OR
  - poor recovery from first relapse
- For use in patients with active disease who want to get pregnant (i.e., use of a temporary therapy to get control of disease, with no need for ongoing therapy which might harm the fetus)
- In cases of older (>50yo) onset disease (i.e., long silent period, with major first event representing significant disease), to limit exposure to long-term immunosuppression
- Patients who are very small or very large (i.e., where weight might impact toxicity/efficacy with standard dose therapies), Mavenclad is the only weight-based MS therapy
- Patients who have a very high likelihood of non-compliance and, thus, challenges in getting control of highly active disease (e.g., schizophrenia)
- Patient is being managed by an experienced MS expert working in an CNMSG-affiliated MS clinic

Suggested exclusion criteria:

- Currently pregnant
- Malignancy (current or recent)
- Active/chronic infection
- EDSS of ≥7.0

Natalizumab (Tysabri)

Suggested criteria for use:

- For use in patients who are and have multiple poor prognostic factors
  - high burden on diagnostic MRI at baseline

  AND
  - severe first relapse

  OR
  - poor recovery from first relapse
- Patient is being managed by an experienced MS expert working in an CNMSC-affiliated MS clinic

Suggested exclusion criteria:

- Malignancy (current or recent)
- Active/chronic infection
- EDSS of ≥7.0
- (+/- in pregnancy; some limited data re: safety in pregnancy, so could be considered)

CNMSC Response to CADTH 1L review

Name of Organization: Canadian Network of MS Clinics (CNMSC)

Primary contact: Dr. Dalia Rotstein, Neurologist - St. Michael's Hospital, Assistant Professor - Department of Medicine, Division of Neurology, University of Toronto [redacted]

Project: Alemtuzumab, Cladribine, Fingolimod, and Natalizumab as First-Line Treatments in Adult Patients With Highly Active Relapsing Multiple Sclerosis

Project number: HT0038-000

Report link: https://www.cadth.ca/sites/default/files/hta-he/HT0038_Draft%20Report_For%20Stakeholder%20Feedback.pdf

Deadline for feedback: 2024-03-21T23:59:59

Feedback page link: Alemtuzumab, Cladribine, Fingolimod, and Natalizumab as First-Line Treatments in Adult Patients With Highly Active Relapsing Multiple Sclerosis - Draft Science Report - HT0038 | CADTH

Introduction

The following feedback is provided on behalf of the Canadian Network of Multiple Sclerosis (MS) Clinics (CNMSC; https://cnmsc.ca/), a national network of academic and community-based clinics established for the advancement of patient services, education, and research in MS.

CNMSC appreciates the opportunity to provide comments and context as it relates to CADTH's draft report regarding the role of alemtuzumab, cladribine, fingolimod, natalizumab, and rituximab as first-line (1L) treatments in adults living with highly active relapsing MS. Having options readily available for select patients with aggressive disease is critical in our efforts as practitioners to avoid serious disability associated with this form of MS.

CNSMC has been actively involved in providing input to this project, having made submissions in February 2022 and October 2023. We hope that the insights provided herein are helpful in finalizing this report.

General Comments

CNMSC is pleased to see CADTH acknowledge that the optimal management of MS has evolved significantly. Specifically, as it relates to those with highly active relapsing MS, we appreciate the recognition of the unmet need and the importance of providing access to early high-efficacy treatment as a means of mitigating the development of rapid disability accumulation in this subgroup of individuals.

The report cites the Canadian Treatment Optimization Recommendations,[1] which speak to the importance of optimal treatment as early as possible – for all individuals with MS, but particularly those with highly active disease. We know that achieving disease control as quickly as possible results in mitigation of disability and/or worsening disease in the long-term, which ultimately benefits health

[1] Freedman M et al. (2020). Treatment Optimization in Multiple Sclerosis: Canadian MS Working Group Recommendations. Canadian Journal of Neurological Sciences, 1-19. doi:10.1017/cjn.2020.66he

outcomes in persons living with MS (PLWMS), as well as direct (i.e., health system) and indirect (i.e., productivity, social assistance) costs.

The report indicates that provincial payers raised this issue as an important policy question that they need to address. As such, CNMSC believes that it is important for CADTH's report to provide insights on the full body of evidence available in order for public (i.e., federal/provincial/territorial government) drug plan managers to make informed decisions on how to translate this report into reimbursement policy changes. It is in the spirit of guiding these decision makers by interpreting the evidence which should inform policy change that the following comments are provided by our organization.

Despite challenges identified vis-à-vis the evidence base, it is critical that payers move forward promptly and leverage the full scope of evidence available to provide access to these medications to mitigate the serious negative impact/permanent disability of the highly active form of MS.

Finally, as the CADTH report notes, the current escalation approach to MS medication access embedded in government drug program reimbursement criteria is no longer consistent with the evolution of the science and globally accepted standards for disease management in MS. While this change in treatment strategy is a larger issue, this report could serve as a starting point for provincial dialogue related to modernizing and aligning criteria for MS products. We believe there is an opportunity for CADTH to work with provinces, CNMSC, and MS Canada to re-assess the reimbursement approach to all MS medications at a national level. This sort of convening activity would be an important function for CADTH as it evolves toward its role as the Canadian Drug Agency.

Feedback Questions:

1. Is the information contained within the report complete? Are there any inconsistencies in the report, or is any relevant information missing?

- In its previous submissions, CNMSC provided a long list of studies that were relevant to the clinical question at hand.
- Unfortunately, the CADTH report only focused on a very limited portion of the evidence base – namely, post-hoc subgroup analyses of 5 randomized controlled trials (RCTs) and 1 prospective comparative cohort study identified through their systematic search and selection procedure.
    - CNMSC believes that the full body of evidence should have been summarized in the report to provide drug plan managers with the information they need to inform the policy decision they need to make.
- The report frequently notes that studies are not stratified for the presence of highly active MS disease.
    - CNMSC provided a clear definition for highly active MS as well as an explanation for the absence of stratification in its October 2023 submission (i.e., the "highly active disease" terminology is relatively recent and, as a result, it has not traditionally been used as a selection criterion to design specific trials in this population).
    - Examination of individuals with highly active disease *a priori* was not a consideration at the time of most of the original studies, as the science had not evolved sufficiently to identify this as a relevant subgroup that should be carved out for specific/differential examination.
    - While the report hints at this issue at the bottom of page 34, this should be clarified/explained more thoroughly, as it speaks to the evolution of the science underpinning our understanding MS. Failure to do so leaves the reader with the impression that the "highly active" subgroup is being fabricated, rather than being based in a refinement in our understanding of MS over the years.

- The bottom-line conclusions outlined on page 33 (Interpretation of Clinical Results from the Systematic Review) – particularly those related to clinician expert perceptions – should be highlighted more clearly in the summaries at the beginning of the report.
    - These clinician perspectives are helpful to payers as the latter determine how they will translate the results of the report into policy decisions regarding the reimbursement status of each of the drugs evaluated.

2. Are there any knowledge mobilization tools that you would like to see created based on this report?

- The recommendations made are very vague and may not be helpful to payers who have to make a decision on whether or not to fund these products.
    - Payers requested that this project be carried out, to address a highly relevant and on-going policy question.
    - As such, payers are looking for clear direction on how their policies should change, based on the evidence available. This level of clarity is not achieved in this report.
    - The report needs to go beyond summarizing a narrow range of the available evidence and should also be more precise in terms of the recommendations based on this evidence.
    - For instance, the report needs to be more clear on its bottom-line conclusion that there is value in funding product X, Y, and/or Z in highly active MS so that payers can implement the results.
    - CNMSC believes that there is sufficient evidence to make statements/recommendations that are more precise than what have been proposed in the draft report.
- The recommendations to payers should also be more precise in terms of defining criteria for leveraging these products in highly active MS.
    - CNMSC provided suggested criteria in its submissions in both February 2022 and October 2023, based on the full body of available evidence as well as the 2020 Canadian Treatment Optimization Recommendations referenced in the CADTH report.

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

- As noted above, the use of the "highly active disease" terminology is relatively recent and clinical trials have not traditionally stratified their populations based on this criterion.
    - Real-world evidence (RWE) has played an important role in addressing this data gap and increasing our understanding of the differential needs and outcomes in this subgroup of PLWMS.
- Unfortunately, the protocol used for CADTH's review excluded RWE and the report itself only superficially addressed the scope of RWE available in the literature (bottom of page 35).
- As an organization, CADTH is emphasizing the importance of RWE as part of its processes. Unfortunately, it has failed to integrate such information in a meaningful way into the evidence evaluation and/or recommendations for this report.
- This is disappointing, as those results are quite compelling and are highly relevant to the policy question at hand.
    - It is very challenging to address these kinds of policy questions through traditional RCTs.
    - The pragmatic RCTs that are being carried out will not be reported for many years – patients with highly active MS cannot wait for these results and need access to these treatments now.
    - As noted above, CADTH needs to make sure that it is leveraging all available evidence to provide advice to payers on the policy questions that they raise.

- The report should put more emphasis on and provide a more detailed summary of the available RWE, so that payers can consider this information as part of their policy deliberations.
    - To address the policy question that drove this analysis and report, CADTH's customers (i.e., payers) need to understand the full scope of evidence available, with appropriate caveats. This means that CADTH needs to look beyond "perfect" evidence and report on the whole picture.

CNMSC Submission - Alemtuzumab, cladribine, fingolimod, and natalizumab as first-line treatments in patients with highly active relapsing MS

Introduction:

The following submission is made on behalf of the Canadian Network of Multiple Sclerosis (MS) Clinics (CNMSC; https://cnmsc.ca/), which is a national network of academic and community-based clinics established for the advancement of patient services, education, and research in MS.

The CNMSC welcomes the opportunity to provide input into CADTH's review of alemtuzumab, cladribine, fingolimod, and natalizumab as first-line treatments in patients with highly active relapsing MS (project number: DR0087-000). Having options readily available for select patients with aggressive disease is critical in our efforts to avoid serious disability associated with this form of MS.

This submission is comprised of 2 parts: a) responses to the specific questions raised by CADTH; and, b) an evidence-based briefing regarding the importance of access to highly-active therapies in patients with aggressive disease. CNMSC looks forward to providing further input as this project moves forward.

The following summarizes the CNMSC's high-level recommendations for 1L line use of the agents in the scope of CADTH's project. More detailed recommendations are included in the briefing section.

CNMSC recommends the following:

1. Drug plans should adopt a more flexible approach that allows the use of higher-efficacy products as first line agents for the treatment of MS patients who present with more aggressive forms of disease.
   - This would recognize that there is a small percentage of patients who warrant an aggressive, early treatment approach to prevent significant disability in the short- and long-term.
   - This would also recognize that experienced MS neurologists need access to these more effective therapies earlier on for such patients.

2. Drug plans should strongly consider the criteria espoused by the TORs for escalation of treatment to a higher-efficacy agent, given that this is considered the best contemporary standard of care.
   - Experienced MS neurologists are in the best position to determine the appropriateness of treatment escalation for their patients.
   - In addition, some of these agents should be considered as initial or induction therapies for patients presenting with high disease activity, aggressive, or rapidly-evolving MS at onset.

3. Drug plans should adopt the proposed approach for case-by-case access to Tysabri, Mavenclad, and Lemtrada in the 1L setting based on the rationale, evidence, and proposed criteria outlined herein.

A) CADTH Questions:

1. Do you think that the project as proposed in the project scope document will be useful to those making policy or clinical practice decisions? Why or why not?

- CNMSC hopes that this review will be useful for policy decisions that will enable the timely use of highly-active therapies in patients with aggressive disease. Time is of the essence for these individuals, as delays in access to treatment can result in significant disability.

2. Are there policy, practice or research questions not considered in the project scope that are required to change or influence practice? If so, what would these be?

- CNMSC agrees that it is important to examine the clinical evidence associated with highly-active agents and their role as 1L therapies for aggressive disease.
- At the same time, CNMSC also believes that it is important to examine reimbursement process barriers that impede timely access to these medications. It is not helpful to have criteria that enable 1L access while at the same time drug program processes are delaying timely reimbursement. Such administrative delays only contribute to the high risk of disability in this vulnerable patient population.

3. Do you have any suggestions for improving the project as proposed in the project scope document?

- See response to Q2 above, as well as the briefing information below.

4. Please provide any additional comments you may have about this document or the project itself, including any studies you think should be included in our review. (A list of included studies and the final project protocol will be posted at a later date.)

- See briefing information below.

B) Briefing Information:

a) Rationale for use of 1L higher-efficacy medications in aggressive MS

It is important to understand that not all MS patients present early with mild disease, the latter of which is more amenable to the more typical sequential escalation approach to therapy. There are also some patients who accumulate silent damage for many years before actually presenting with their first MS symptoms. It is imperative that these patients be treated differently, as they are already more advanced in the disease process than typical MS patients.

Historic data show that patients with highly-aggressive MS are at significant risk of early disability worsening and poor long-term MS outcomes, making the identification and prompt treatment of these patients with higher-efficacy disease-modifying therapies (DMTs) particularly important. This is a small patient population and represents less than 5 percent of newly diagnosed MS patients. In terms of potential utilization of Mavenclad 1L and/or Tysabri 1L, and/or Lemtrada 1L in Ontario MS clinics, for instance, this would probably represent approximately 100 patients per year requiring these high-efficacy treatments for their aggressive disease.

The ***2020 Treatment optimization in multiple sclerosis: Canadian MS Working Group recommendations (TORs)***[1] specifically speak to the importance of using higher efficacy treatments in patients presenting with more aggressive disease, based on the rationale that taking the traditional sequential escalation approach (i.e., trying and likely failing to control the disease with regular 1L medications in order to access higher-efficacy therapies) causes irreversible and probably preventable damage to the nervous system.

A recent analysis[2] examined the costs and benefits of "front-loading" the cost of treatment for MS by using more expensive and effective treatments earlier on (i.e., the concept of earlier treatment with more highly active therapies). Modelling and cost-effectiveness analysis supported the hypothesis that using more aggressive measures earlier on may result in a reduction in the cost of long-term disability associated with MS.

The information below provides an overview of the rationale for using highly-active products in the 1L setting in patients with aggressive disease. Summaries of the rationale for the use of Mavenclad 1L, Tysabri 1L, and Lemtrada 1L in selected patients are also provided, including proposed criteria and a summary of the available evidence for each. It is hoped that this provides sufficient information for the drug plans to move forward with developing criteria and providing access to these products in the 1L setting.

b) Patient Identification

From a demographic perspective, patients at risk of a more aggressive clinical course, worse outcomes, and/or a poorer response to DMTs include males, individuals of non-white ethnicity, and those with high-risk clinical/radiological or biomarker disease factors.

From a clinical perspective, the following are some of the major signs and symptoms that are reflective of more aggressive disease and are prognostic of a worse clinical course and poorer long-term outcomes in CIS and RMS.

- Evidence of highly active disease (e.g. frequent relapses, high burden of disease on MRI at onset, or new MRI lesions in a short time period);
- Extensive CNS involvement (clinical evidence of widespread disease along with multifocal, lesion number and location, T2 burden of disease on MRI);
- Inadequate recovery/repair (residual impairment, higher baseline EDSS score) post-relapse; and/or,
- Early cognitive involvement.

c) Choosing Medications – General Principles

As a general principle, the choice of 1L medication for a patient with MS needs to be tailored based on their clinical presentation, the aggressiveness of their disease, comorbidities, and other relevant factors. The information in Table 1 outlines the approach to decision making when considering the use of a higher-efficacy agent in the 1L setting in patients with aggressive disease. The four products in scope for the CADTH review are included, as well as other products used in the first line setting.

[1] Freedman M et al. (2020). Treatment Optimization in Multiple Sclerosis: Canadian MS Working Group Recommendations. Canadian Journal of Neurological Sciences, 1-19. doi:10.1017/cjn.2020.66

[2] Batcheller L and David Baker D. Cost of disease modifying therapies for multiple sclerosis: Is front-loading the answer? Journal of the Neurological Sciences 2019; 404(9): 19-28. https://doi.org/10.1016/j.jns.2019.07.009

Table 1. Overview of various products used in the 1L setting.

Product	Attributes and clinical decision-making considerations
Tysabri (natalizumab)	• A high efficacy therapy with the most rapid onset of action. ○ Superiority has not been tested against a 1L treatment in a large phase III trial similar to other agents below. • In cases of aggressive disease, it can be used to gain quick control of disease with a view to a more definitive treatment. • Rapid onset benefit may be offset by a high burden for PML monitoring and serious concerns for rebound disease upon cessation for any reason. • Administration burden may be onerous, with infusions every 4-6 weeks. • Patients who have low titre antibodies to the JCV may be at a lower risk for getting PML, but the antibody titres tend to increase with continued treatment and ultimately can lead to cessation for fear of a high risk to get PML. • Concern regarding rebound on cessation of treatment, especially for pregnancy.
Immune Reconstitution Therapies (IRTs) • This category includes Mavenclad and Lemtrada. • Both agents are given as an induction course in the 1st year, followed by a prolonged period of no required treatment, allowing the "reconstitution" of the immune system before a repeat treatment in the following year. • Both therapies have been shown to produce a durable response requiring no further treatments for up to 4 years. Beyond 4 years, repeat treatments might be necessary should the disease re-surface. There is no need to follow these treatments with traditional 1L treatments. • Because they do not need to be persistently given, there is no risk for PML, unlike Tysabri. • Women interested in having families can safely do so 6 months following the 2nd year's treatment (effectively 18 months from the 1st course of treatment).	
Mavenclad (cladribine)	• Given as an induction course in the 1st year over 1 week for 2 consecutive months, with repeat treatment in the following year over 1 week for 2 consecutive months • Provides quick control over the patient's disease • Also offers the ability to stop treatment (i.e., time-limited treatment) and still achieve a long-term/durable effect • Preferred role in patients with active disease who want to get pregnant (i.e., after they finish their 2-year course of treatment) ○ Most other MS drugs are problematic in this patient population (planning pregnancy) because of teratogenicity and/or disease rebound on discontinuation of the drug during the period of conception/gestation.
Lemtrada (alemtuzumab)	• Given as an induction course in the 1st year over 5 consecutive days, with repeat treatment in the following year over 3 days • Due to more inherent side effects, Lemtrada has been less favoured for 1L treatment of aggressive MS, yielding to Mavenclad as the favoured agent.
B cell directed therapies • Includes ocrelizumab, rituximab, and emerging therapies (i.e., ofatumumab, ublituximab [not likely to be submitted to HC for approval] • All B cell directed therapies are proven to be higher efficacy and are already or will soon be available for 1L use. • Thus far, all need to be given regularly to be effective, but long term safety due to significant immunosuppression is a concern. • It is not clear whether they can be stopped and still sustain continued efficacy (i.e. a durable response, similar to the IRT). • They are thus far not associated with rebound disease, but still have the potential for causing PML, although much less compared with Tysabri.	
Ocrevus	• A higher efficacy partially humanized monoclonal antibody therapy available 1L • May not be appropriate for all patients (e.g., those with breast cancer, hepatitis)
Kesimpta	• Newly approved fully humanized monoclonal antibody therapy with similar clinical effects to Ocrevus. • Patient advantage over Ocrevus in not requiring infusion centres, as it is given by self-injection monthly • More rapid return of B cell counts upon cessation compared to Ocrevus

S1P Receptor Agonists
• Gilenya (and fingolimod generics), Ponvory, Zeposia (and Mayzent) are all approved for treatment of RMS
  ○ (Mayzent is only approved for treatment of active SPMS)
  ○ Ponvory and Zeposia are approved for 1L treatment, raising concern as to why Gilenya is not for adults, since it is approved 1L for children; therefore, we will consider this to be an anomaly that will be corrected and we will consider the entire group as available 1L
• Similar to Tysabri, onset of action is rapid and efficacy proven superior to IFNbeta or teriflunomide. (Tysabri was never studied in a large head to head study vs. another agent.)
• Gilenya requires first dose monitoring whereas Ponvory and Zeposia do not.	

Product	Attributes and clinical decision-making considerations
• Monitoring for opportunistic infections important, with PML noted with Gilenya, especially in older patients (>50); PML not noted as yet with Ponvory or Zeposia • Monitoring for potential for macular edema advised after 3 months of treatment • Should be carefully considered for patients with co-morbidities such as diabetes (higher risk for conditions such as uveitis or macular edema) • Similar to Tysabri, rebound disease upon cessation of Gilenya can be rapid (within 3 months) and severe, necessitating a mitigation strategy should discontinuation be required due to adverse event or desire for pregnancy (given proven teratogenicity); rebound disease thus far not seen for either Ponvory or Zeposia. • These agents are also considered higher efficacy but unlike either Tysabri, Mavenclad or Lemtrada, were unable to demonstrate superiority over 1L treatments in terms of disease progression (only on ARR and MRI activity)	
Gilenya (and generics)	• Currently semi-approved as 1L (HC wording "generally not given first line", essentially allows it to be given 1L) • Approved 1L for children • Required 1st dose monitoring for bradycardia • Monitoring for macular edema after 3 months • High potential for rebound disease (often severe) after cessation of treatment, making it a poor choice for patients planning imminent pregnancy • Potential for PML a concern after long term treatment in older patients (>50) • Prolonged half like (~7 days) • Takes ~3 months for lymphocyte counts to return to normal
Zeposia	• Approved by HC for 1L treatment • Thus far appears safer than Gilenya, but long term and real world data not yet available • No need for 1st dose monitoring owing to the type of drug (more specific to receptors) and dose titration • Monitoring for macular edema at 3 months, but incidence appears less than Gilenya • Rebound disease not yet observed, but limited data available • Drug metabolite can cause a long half-life to 3-6 months • May offer benefit in terms of cognitive improvement
Ponvory	• Similar to Zeposia except for differences noted below • May offer benefit to patients with severe fatigue • Half life the shortest at ~30 hours

d) Specific Recommendations for Specific MS Medications

i) Mavenclad 1L

The following provides a summary of the rationale for the use of Mavenclad 1L in selected patients, proposed criteria, and a summary of the available evidence. It is hoped that this provides sufficient information to move forward with developing criteria and providing access to Mavenclad in the 1L setting.

Rationale:

- Mavenclad provides highly-effective control over the patient's disease and also offers the ability to stop treatment (i.e., time-limited treatment) while still achieving a long-term/durable effect.
    - The approach to dosing of Mavenclad is unique, in that patients are treated for a limited period of time (i.e., 1 week of treatment for 2 consecutive months, once a year for a total of 2 years)
- There is evidence supporting the use of Mavenclad in the 1L setting of CIS, with evidence of benefit in decreasing long-term disability (see Appendix I). No other higher-efficacy therapy has such evidence in CIS.

  - The data generated for Mavenclad provide evidence that treatment with a high-efficacy medication in the 1L setting improves clinical outcomes.
  - Long-term data from the CLARITY study have shown that the effects of Mavenclad last 2- 4 years (after the 2-year treatment course).
- There is also evidence to support the use of Mavenclad 1L in cases where patients present with factors that are indicative of highly-aggressive disease.
  - Use would be in those cases where patients have presented seemingly late with their disease and have acquired already significant disease burden.
  - NOTE: the choice of 1L drug for patients with highly-aggressive disease is based on the individual needs of the patient, co-morbidities, etc.
- There is also a unique role for Mavenclad in patients with active disease who want to get pregnant (i.e., after they finish their 2-year course of treatment)
  - Most other MS drugs are problematic in this patient population because of teratogenicity and/or disease rebound on discontinuation of the drug during the period of conception/gestation.
  - There is a substantial safety registry for Mavenclad, which has demonstrated that the drug has very few side effects compared to other “induction” drugs (e.g., Lemtrada).
- Overall, the use of Mavenclad 1L would represent a small patient population (see above – less than 5% of newly diagnosed patients).
- Use of Mavenclad in 1L may be less costly than the current use of other 1L DMTs.

<u>Suggested drug plan approach:</u>
- Consider requests for Mavenclad 1L on a case-by-case basis
- Requests should be restricted to experienced MS experts working in an MS clinic affiliated with the CNMSC
- 1-year approval period is sufficient (as these patients are followed very closely)

<u>Suggested Criteria for Use:</u>
- For use in patients who are and have multiple poor prognostic factors
  - high burden on diagnostic MRI at baseline
    AND
  - severe first relapse
    OR
  - poor recovery from first relapse
- For use in patients with active disease who want to get pregnant
- Patient is being managed by an experienced MS expert working in an CNMSC-affiliated MS clinic

ii) Tysabri 1L

The following provides a summary of the rationale for the use of Tysabri 1L in selected patients, proposed criteria, and a summary of the available evidence. It is hoped that this provides sufficient information to move forward with developing criteria and providing access to Tysabri in the 1L setting.

Rationale:
- The evidence supporting the use of Tysabri is all in the 1L setting.
- There is also evidence to support the use of Tysabri 1L in cases where patients present with factors that are indicative of highly-aggressive disease.
- Use would be in those cases where time is of the essence re: getting the patient's disease under control in order to prevent significant detrimental disease impacts.
- In these cases, there is a need for medication with a very rapid onset of effect (like Tysabri) that can bring aggressive disease under control quickly (NOTE: Tysabri shuts down the disease by closing off the blood-brain barrier).
- Overall, the use of Tysabri 1L would represent a small patient population (see above – less than 5% of newly diagnosed patients).

Suggested drug plan approach:
- Consider requests for Tysabri 1L on a case-by-case basis
- Requests should be restricted to experienced MS experts working in an MS clinic affiliated with the CNMSC
- 1-year approval period is sufficient (as these patients are followed very closely)

Suggested Criteria for Use:
- For use in patients who are and have multiple poor prognostic factors
    - high burden on diagnostic MRI at baseline
      AND
    - severe first relapse
      OR
    - poor recovery from first relapse
- Patient is being managed by an experienced MS expert working in an CNMSC-affiliated MS clinic

iii) Lemtrada 1L:

The following provides a summary of the rationale for the use of Alemtuzumab 1L in selected patients, proposed criteria, and a summary of the available evidence. It is hoped that this provides sufficient information to move forward with developing criteria and providing access to Lemtrada in the 1L setting.

Rationale:
- Lemtrada provides highly-effective control over the patient's disease and also offers the ability to stop treatment (i.e., time-limited treatment) while still achieving a long-term/durable effect.
    - The approach to dosing of Lemtrada is unique, in that patients are treated for a limited period of time (i.e., 5 days of consecutive treatment in the 1st year and 3 consecutive days in year 2)
    - Further courses of 3-day treatments are allowed beyond year 3 (1 year following the last treatment) in response to recurrent disease
- Lemtrada is the only higher efficacy therapy actually proved to be more effective than IFN-beta in patients already established to have breakthrough disease (CARE MS II trial)

- Monitoring for potential autoimmune conditions is intensive (monthly for 4 years subsequent to the last treatment)
- More recent reports of hypertensive intracerebral hemorrhage or stroke strikes additional cautions for use of this agent.
- May also be a useful approach for quelling aggressive disease quickly to allow for pregnancy, during which no further treatment is necessary (similar to Mavenclad)

Suggested drug plan approach:
- Consider requests for Lemtrada 1L on a case-by-case basis
- Requests should be restricted to experienced MS experts working in an MS clinic affiliated with the CNMSC
- 1-year approval period is sufficient (as these patients are followed very closely)

Suggested Criteria for Use:
- For use in patients who are and have multiple poor prognostic factors
    - high burden on diagnostic MRI at baseline
      AND
    - severe first relapse
      OR
    - poor recovery from first relapse
- For use in patients with active disease who want to get pregnant
- Patient is being managed by an experienced MS expert working in an CNMSC-affiliated MS clinic

C) Summary of Evidence:

- The studies outlined in Table 2 speak to the evidence for the use of Mavenclad, Tysabri, and Lemtrada in the first line setting.
- In addition, review articles are included that discuss the clinical and economic rationale for aggressive treatment of MS.

Table 2. Evidence related to 1L use of highly-efficacious MS treatments

Study	Design	Results
Mavenclad clinical trials		
Giovannoni G et al. A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis (CLARITY). NEJM January 20, 2010. 10.1056/NEJMoa0902533	• Phase 3, 96-wk short-course oral tablet therapy in RRMS • Received one of two cumulative doses of cladribine over 96 weeks (either 3.5 mg or 5.25 mg/kg) administered orally as short courses, given once daily for the first 4 or 5 days of a 28-day period	• Lower annualized rate of relapse vs. placebo (0.14 and 0.15 vs. 0.33; P<0.001) • Higher relapse-free rate (79.7% and 78.9% vs. 60.9%; P<0.001) • Lower risk of 3-month sustained progression of disability (HR 3.5-mg group, 0.67; 95% [CI] 0.48-0.93, P = 0.02); (HR 5.25-mg group, 0.69; 95% CI, 0.49-0.96; P = 0.03) • Significant reductions brain lesion count on MRI (P<0.001) • Of note, a subset of the CLARITY study (said to have highly-active disease) showed even greater efficacy compared with overall study

Study	Design	Results
		population. This analysis was a key part of the European regulatory approval.
Giovannoni G et al. Safety and efficacy of cladribine tablets in patients with relapsing–remitting multiple sclerosis: Results from the randomized extension trial of the CLARITY study. Multiple Sclerosis Journal. July 2017: 1–11. DOI: 10.1177/1352458517727603	• Phase 3b 2y extension trial • Placebo recipients from CLARITY received cladribine 3.5 mg/kg; cladribine recipients were re-randomized 2:1 to cladribine 3.5 mg/kg or placebo, with blinding maintained	• Cladribine tablets treatment for 2 years followed by 2 years' placebo treatment produced durable clinical benefits similar to 4 years of cladribine treatment with a low risk of severe lymphopenia or clinical worsening. • No clinical improvement in efficacy was apparent following further treatment with cladribine tablets after the initial 2-year treatment period in this trial setting.
Comi G et al. Long-term effects of cladribine tablets on MRI activity outcomes in patients with relapsing–remitting multiple sclerosis: the CLARITY Extension study. Ther Adv Neurol Disord 2018, Vol. 11: 1– 11. DOI: 10.1177/1756285618753365	• Key MRI from the CLARITY Extension study • MRI assessments carried out when patients entered CLARITY Extension + after Weeks 24, 48, 72 and 96, and in a supplemental follow-up period	A 2-year treatment with CT 3.5 mg/kg has a durable effect on MRI outcomes in the majority of patients, an effect that was sustained in patients who were not retreated in the subsequent 2 years after initial treatment
Leist TP et al. Effect of oral cladribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE MS): a phase 3 randomised trial. Lancet Neurol 2014; 13: 257–67 http://dx.doi.org/10.1016/S1474-4422(14)70005-5	• Effect of oral cladribine on conversion to clinically definite MS in patients with a first clinical demyelinating event • P3 96wk RCT comparing cladribine tablets at cumulative doses of 5.25 mg/kg or 3.5 mg/kg vs. placebo	• Cladribine associated with a risk reduction versus placebo for time to conversion to clinically definite MS (HR 5.25 mg/kg=0.38, 95% CI 0.25–0.58, p<0·0001; HR 3.5 mg/kg=0.33, 0.21–0.51, p<0·0001) • Both doses of cladribine significantly delayed MS diagnosis compared with placebo • Safety profile of cladribine was similar to that noted in a trial in patients with RRMS
Freedman MS et al. The efficacy of cladribine tablets in CIS patients retrospectively assigned the diagnosis of MS using modern criteria: Results from the ORACLE-MS study. Multiple Sclerosis Journal - Experimental, Translational and Clinical. October-December 2017: 1-14. DOI: 10.1177/ 2055217317732802	• Efficacy of cladribine tablets in CIS patients retrospectively assigned the diagnosis of MS using modern criteria (in ORACLE-MS study) • Post-hoc analysis for subgroups of patients retrospectively classified as fulfilling or not fulfilling newer criteria at the first clinical demyelinating attack • 223 of 616 patients (36.2%) in ORACLE MS would have met the diagnosis of MS vs CIS using the newer criteria	• 3.5 mg/kg (n=68) reduced risk of next attack or three-month confirmed EDSS worsening by 74% vs placebo (n=72) p= 0.0009 in patients meeting newer criteria for MS at baseline • 5.25 mg/kg (n=83) reduced risk of next attack or three-month confirmed EDSS worsening by 37% but NS (p=0.14) • In patients who were still CIS after applying newer criteria, 3.5 mg/kg • (n=138) reduced the risk of conversion to clinically definite multiple sclerosis (CDMS) by 63% vs placebo (n=134) p=0.0003; 5.25 mg/kg (n=121) reduced the risk of conversion by 75% vs placebo (n=134) p<0.0001 • Regardless of the criteria used to define CIS or MS, 3.5 mg/kg cladribine is effective in patients with a first clinical demyelinating attack
Montalban X et al. Cladribine tablets added to IFN-β in active relapsing MS: The ONWARD study. Neurology: Neuroimmunology & Neuroinflammation; 2018;5(5):e477. doi:10.1212/NXI.0000000000000477	• Evaluate the safety and efficacy of cladribine tablets in patients still experiencing active relapsing MS despite IFN-β treatment • 96-week P2 study	cladribine 3.5 mg/kg+IFN-β reduced relapses and MRI lesion activity over 96 wk vs. placebo+IFN-β but led to an increased incidence of lymphopenia
Tysabri clinical trials		
Polman CH et al. A Randomized, Placebo-Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis (AFFIRM). N Engl J Med 2006;354:899-910.	• two-year phase 3 trial • patients 18-50yo diagnosed with relapsing MS with no previous treatment • ESDD of 0 to 5.0; MRI showing lesions consistent with MS	• Natalizumab reduced the risk of sustained progression of disability by 42% over two years (HR 0.58; 95% CI 0.43 to 0.77; P<0.001) • cumulative probability of progression was 17% vs. 29% with placebo • reduced rate of clinical relapse at 1y by 68% (P<0.001)

Study	Design	Results
	• at least one medically documented relapse within the 12 months before the study began • 942 patients; 627 randomly assigned to receive natalizumab (300 mg) and 315 to receive placebo IV q4w for more than two years. • primary end points = rate of clinical relapse at 1y; rate of sustained progression of disability, as measured by EDSS at 2y	• 83% reduction in accumulation of new or enlarging hyperintense lesions, as detected by T2-weighted MRI, over 2y (mean numbers of lesions, 1.9 with natalizumab and 11.0 with placebo; P<0.001) • 92% percent fewer lesions (as detected by gadolinium-enhanced MRI) in the natalizumab group than in the placebo group at both 1 and 2y (P<0.001) • AEs that were significantly more frequent vs. placebo group were fatigue (27% vs. 21%, P = 0.048) and allergic reaction (9% vs. 4%, P = 0.012) • Hypersensitivity reactions of any kind: 25 patients receiving natalizumab (4%), and serious hypersensitivity reactions occurred in 8 patients (1%). Summary: Natalizumab reduced the risk of the sustained progression of disability and the rate of clinical relapse in patients with relapsing MS.
Wiendl H et al. Epoch Analysis of On-Treatment Disability Progression Events over Time in the Tysabri Observational Program (TOP). PLoS ONE 11(1): e0144834. doi:10.1371/journal.pone.0144834 Published: Jan 15/16	• Observational study • To evaluate the effect of natalizumab on disability progression beyond 2 years of treatment in clinical practice • 496 RRMS patients among 5122 patients in the Tysabri Observational Program (TOP) who had completed 4 continuous years of treatment and had baseline (study enrollment) and postbaseline EDSS) assessments. • Proportions of patients with 6-month or 12-month confirmed ≥1.0-point EDSS progression relative to baseline were compared in treatment months 1–24 and 25–48. • Sensitivity analyses compared progression rates in months 13–24 and 25–36.	• Baseline characteristics similar between the overall TOP population (N = 5122), patients who had completed 4 years of natalizumab treatment (n = 469), and patients eligible to complete 4 years in TOP who had discontinued natalizumab after 2 years of treatment (n = 514). • Among 4-year completers, the proportion of patients with 6-month and 12-month confirmed EDSS progression decreased between months 1–24 and 25–48 of natalizumab treatment by 42% (from 10.9% to 6.3%; p < 0.01) and 52% (from 9.5% to 4.6%; p < 0.01), respectively. • Few patients had 6-month or 12-month confirmed EDSS progression in both epochs (0.6% and 0.2%, respectively). • Between months 13–24 and 25–36 of treatment, the proportion of patients with 6-month and 12-month confirmed EDSS progression decreased • by 60% (from 7.5% to 3.0%; p < 0.01) and 58% (from 6.7% to 2.8%; p < 0.01), respectively. • Significant reductions in disability progression events between months 13–24 and 25–36 • were also observed in relapse-free patients Summary: • disability progression rate decreased further beyond 2y of natalizumab treatment. • Patients who responded well and remained on continuous natalizumab therapy for over 4 years had sustained and potentially enhanced reductions in EDSS progression over time.
Lemtrada clinical trials		
Cohen JA et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial (CARE-I). Lancet 2012; 380: 1819–28. http://dx.doi.org/10.1016/S0140-6736(12)61769-3	• 2 year, rater-masked, Phase 3 RCT • adults aged 18–50 years with previously untreated RRMS • randomly allocated in a 2:1 ratio to receive IV alemtuzumab 12 mg per day (once per day for 5 days at baseline and once per day for 3 days at 12 months) or SC interferon beta 1a 44 µg 3x/w • Coprimary endpoints: relapse rate and time to 6 month sustained accumulation of disability	• 75 (40%) patients in the interferon beta 1a group relapsed (122 events) compared with 82 (22%) patients in the alemtuzumab group (119 events; rate ratio 0.45 [95% CI 0.32–0.63]; p<0.0001), corresponding to a 54.9% improvement with alemtuzumab • 59% of patients in the interferon beta 1a group were relapse-free at 2 years compared with 78% of patients in the alemtuzumab group (p<0·0001). • 20 (11%) of patients in the interferon beta 1a group had sustained accumulation of disability compared with 30 (8%) in the alemtuzumab group (hazard ratio 0·70 [95% CI 0·40–1·23]; p=0·22).

Study	Design	Results
		• 338 (90%) of patients in the alemtuzumab group had infusion-associated reactions; 12 (3%) of which were regarded as serious. Infections, predominantly of mild or moderate severity, occurred in 253 (67%) patients treated with alemtuzumab versus 85 (45%) patients treated with interferon beta 1a. 62 (16%) patients treated with alemtuzumab had herpes infections (predominantly cutaneous) compared with three (2%) patients treated with interferon beta 1a. By 24 months, 68 (18%) patients in the alemtuzumab group had thyroid-associated adverse events compared with 12 (6%) in the interferon beta 1a group, and three (1%) had immune thrombocytopenia compared with none in the interferon beta 1a group. Two patients in the alemtuzumab group developed thyroid papillary carcinoma. Summary: • Alemtuzumab's consistent safety profile and benefit in terms of reductions of relapse support its use for patients with previously untreated relapsing-remitting multiple sclerosis; however, benefit in terms of disability endpoints noted in previous trials was not observed here.
Coles AJ et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial (CARE-II). Lancet 2012; 380(9856):1829-39. http://dx.doi.org/10.1016/S0140-6736(12)61768-1	• 2 year, rater-masked, Phase 3 RCT • adults aged 18–55 years with RRMS and at least one relapse on interferon beta or glatiramer. • randomly allocated in a 1:2:2 ratio to receive SC interferon beta 1a 44 µg, IV alemtuzumab 12 mg per day, or IV alemtuzumab 24 mg per day. Interferon beta 1a was given three-times per week and alemtuzumab was given once per day for 5 days at baseline and for 3 days at 12 months. • Coprimary endpoints were relapse rate and time to 6 month sustained accumulation of disability	• The 24 mg per day group was discontinued to aid recruitment, but data are included for safety assessments. • 104 (51%) patients in the interferon beta 1a group relapsed (201 events) compared with 147 (35%) patients in the alemtuzumab group (236 events; rate ratio 0.51 [95% CI 0.39–0·65]; p<0.0001), corresponding to a 49.4% improvement with alemtuzumab. 94 (47%) patients in the interferon beta 1a group were relapse-free at 2 years compared with 278 (65%) patients in the alemtuzumab group (p<0.0001). • 40 (20%) patients in the interferon beta 1a group had sustained accumulation of disability compared with 54 (13%) in the alemtuzumab group (hazard ratio 0.58 [95% CI 0.38–0.87]; p=0.008), corresponding to a 42% improvement in the alemtuzumab group. • For 435 patients allocated alemtuzumab 12 mg, 393 (90%) had infusion-associated reactions, 334 (77%) had infections (compared with 134 [66%] of 202 patients in the interferon beta 1a group) that were mostly mild-moderate with none fatal, 69 (16%) had thyroid disorders, and three (1%) had immune thrombocytopenia Summary: • For patients with first-line treatment-refractory relapsing-remitting multiple sclerosis, alemtuzumab could be used to reduce relapse rates and sustained accumulation of disability. Suitable risk management strategies allow for early identification of alemtuzumab's main adverse eff ect of secondary autoimmunity.
Hardova E et al. Alemtuzumab CARE-MS I 5-year follow-up: Durable efficacy in the absence of continuous MS therapy. Neurology 2017;89:1107–1116	• evaluate 5-year efficacy and safety of alemtuzumab in treatment-naive patients with active RRMS • after the core study, patients could enter an extension (NCT00930553) with as-needed alemtuzumab retreatment for relapse or MRI activity. • Assessments included annualized relapse rate (ARR), 6-month confirmed disability worsening	• Most alemtuzumab-treated patients (95.1%) completing CARE-MS I enrolled in the extension; 68.5%received no additional alemtuzumab treatment. • ARR remained low in years 3, 4, and 5 (0.19, 0.14, and 0.15). Over years 0–5, 79.7% were free of 6-month CDW; 33.4% achieved 6-month CDI. Most patients (61.7%, 60.2%, and 62.4%) had NEDA in years 3, 4, and 5. Median yearly BVL improved over years 2–4, remaining low in year 5 (years 1–5: 20.59%, 20.25%, 20.19%, 20.15%, and 20.20%).

Study	Design	Results
	(CDW; ≥1-point Expanded Disability Status Scale [EDSS] score increase [≥1.5 if baseline EDSS 5 0]), 6-month confirmed disability improvement (CDI; ≥1-point EDSS decrease [baseline score ≥2.0]), no evidence of disease activity (NEDA), brain volume loss (BVL), and adverse events (AEs).	• Exposure-adjusted incidence rates of most AEs declined in the extension relative to the core study. Thyroid disorder incidences peaked at year 3 and subsequently declined. Summary: • alemtuzumab provides durable efficacy through 5 years in the absence of continuous treatment, with most patients not receiving additional courses.
Coles AJ et al. Alemtuzumab CARE-MS II 5-year follow-up: Efficacy and safety findings. Neurology 2017;89:1117–1126	• evaluate 5-year efficacy and safety of alemtuzumab in patients with active RRMS and inadequate response to prior therapy. • Patients could enter an extension (NCT00930553), with as-needed alemtuzumab retreatment for relapse or MRI activity. • Annualized relapse rate (ARR), 6-month confirmed disability worsening (CDW; ≥1-point Expanded Disability Status Scale [EDSS] score increase [≥1.5 if baseline EDSS 5 0]), 6-month confirmed disability improvement (CDI; ≥1-point EDSS decrease [baseline score ≥2.0]), no evidence of disease activity (NEDA), brain volume loss (BVL), and adverse events (AEs) were assessed.	• Most alemtuzumab-treated patients (92.9%) who completed CARE-MS II entered the extension; 59.8%received no alemtuzumab retreatment. • ARR was low in each extension year (years 3–5: 0.22, 0.23, 0.18). Through 5 years, 75.1% of patients were free of 6-month CDW; 42.9% achieved 6-month CDI. In years 3, 4, and 5, proportions with NEDA were 52.9%, 54.2%, and 58.2%, respectively. Median yearly BVL remained low in the extension (years 1–5: 20.48%, 20.22%, 20.10%, 20.19%, 20.07%). • AE exposure-adjusted incidence rates in the extension were lower than in the core study. Thyroid disorders peaked at year 3, declining thereafter. Summary: • Alemtuzumab provides durable efficacy through 5 years in patients with an inadequate response to prior therapy in the absence of continuous treatment. • This study provides Class III evidence that alemtuzumab provides efficacy and slowing of brain atrophy through 5 years
Willis MD et al. Alemtuzumab for multiple sclerosis: Long term follow-up in a multi-centre cohort. Multiple Sclerosis Journal 2015: 1–9 DOI: 10.1177/1352458515614092	• long-term efficacy and safety outcomes in a multicentre cohort of patients treated with alemtuzumab • Patients treated from 2000 and followed-up at three regional centres were identified. Baseline and prospective data were obtained and validated by clinical record review.	• One hundred patients were identified with a mean follow-up of 6.1 years (range 1–13). Forty patients were retreated with at least one further treatment cycle. Annualized relapse rates fell from 2.1 to 0.2 ($p<0.0001$) post-treatment and were sustained for up to eight years of follow-up. Mean change in EDSS score was +0.14. Forty-seven patients developed secondary autoimmunity. Summary: • Observed reduction in relapse rates reflected those reported in clinical trials, but we were unable to corroborate previous observations of disability reversal. 40% of patients required additional treatment cycles. Autoimmune adverse events were common, occurring at a higher rate than previously reported, but were largely predictable, and could be managed effectively within a rigorous monitoring regime.
Fox EJ et al. Alemtuzumab improves neurological functional systems in treatment-naive relapsing-remitting multiple sclerosis patients. Journal of the Neurological Sciences 363 (2016) 188–194.	• assessed the effect of alemtuzumab on individual functional system scores (FSS) of the Expanded Disability Status Scale (EDSS) • 36-month, rater-blinded, phase 2 trial; treatment-naive patients with active RRMS, EDSS ≤3, and symptom onset within 3 years were randomized to annual courses of alemtuzumab or subcutaneous interferon beta-1a (SC IFNB-1a) 44 µg three times weekly.	• Alemtuzumab-treated patients had improved outcomes versus SC IFNB-1a patients on most FSS at Month 36; the greatest effect occurred for sensory, pyramidal, and cerebellar FSS. Among patients who experienced 6-month sustained accumulation of disability, clinical worsening occurred most frequently in the brainstem and sensory systems. For patients with 6-month sustained reduction in preexisting disability, pyramidal and sensory systems contributed most frequently to clinical improvement. Summary: • Alemtuzumab demonstrated a broad treatment effect in improving preexisting disability. These findings may influence treatment decisions

Study	Design	Results
		in patients with early, active relapsing-remitting MS displaying neurological deficits.
General review articles		

Freedman M et al. (2020). Treatment Optimization in Multiple Sclerosis: Canadian MS Working Group Recommendations. Canadian Journal of Neurological Sciences, 1-19. doi:10.1017/cjn.2020.66	https://www.cambridge.org/core/journals/canadian-journal-of-neurological-sciences/article/treatment-optimization-in-multiple-sclerosis-canadian-ms-working-group-recommendations/6F71BA9F915D7AC1228BBB52EF3B8AD7
	• The Treatment Optimization Recommendations (TOR) are intended to guide the optimal use of disease-modifying therapies (DMT) for patients with all forms of multiple sclerosis (MS).
	• The guidance also speaks to the identification and treatment of aggressive forms of the disease, an area of emphasis because of the critical importance of achieving disease control in these patients.
	  • Patients with highly-aggressive disease are at significant risk of early disability worsening and warrant early treatment with a higher-efficacy DMT.
	  • Patients at risk of a more aggressive clinical course, worse outcomes, and/or a poorer response to DMTs include males, individuals of non-white ethnicity, and those with high-risk clinical/radiological disease factors.
	  • Evidence of highly active disease (e.g. frequent relapses, new MRI lesions), extensive CNS involvement (multifocal, lesion number and location, T2 burden of disease) and/or inadequate recovery/repair (residual impairment, higher baseline EDSS score) or cognitive reserve are prognostic of a worse clinical course and poorer long-term outcomes in CIS and RMS.	

Batcheller L and David Baker D. Cost of disease modifying therapies for multiple sclerosis: Is front-loading the answer? Journal of the Neurological Sciences 2019; 404(9): 19-28. https://doi.org/10.1016/j.jns.2019.07.009	• This review looks at the different DMTs available for MS and attempts to draw some conclusions on their cost-effectiveness. It also considers the costs and benefits of front loading the cost of treatment for MS by using more expensive and effective treatment earlier on. • CEAs support the idea that using more aggressive measures earlier on may mean the cost of long-term disability is reduced.	

Rush, C. A. et al. Aggressive multiple sclerosis: proposed definition and treatment algorithm. Nat. Rev. Neurol. 11, 379–389 (2015); published online 2 June 2015; doi:10.1038/nrneurol.2015.85	Defining 'aggressive' MS:
	  • rampant progression of disability over a short time period
	  • early, unexpected acquisition of disability followed by frequent relapses (often with incomplete resolution) and highly active disease seen on MRI
	  • as any type of MS that is associated with repeated severe attacks and accelerated accrual of disability
	  • We suggest that aggressive MS can be defined as RRMS with **one or more** of the following features:
	  ○ EDSS score of 4 within 5 years of onset
	  ○ Multiple (two or more) relapses with incomplete resolution in the past year
	  ○ More than two MRI studies showing new or enlarging T2 lesions or gadolinium-enhancing lesions despite treatment
	  ○ No response to therapy with one or more DMTs for up to 1 year
	Early identification:
	  • important to identify patients who are at risk of aggressive MS as early as possible and implement an effective treatment strategy
	  • early intervention might protect patients from irreversible damage and disability, and prevent the development of a secondary progressive course
	  • Population studies have indicated that relapses occurring in the first 2 years of MS drive early disease progression, with diminishing contribution from later relapses (after year 3).
	Approach to management:
	  • window of opportunity for treating patients with aggressive MS is narrow, thus, conventional treatment paradigms need to be reconsidered
	  • Evidence over the past decade points to a window of opportunity for effective treatment in patients with MS, which covers the period of peak CNS inflammation
	  • Current DMTs target the early type of CNS inflammation that is believed to substantially contribute to demyelination and axonal damage. Therefore, these therapies are more effective when the inflammatory process is prevalent, as in the early stages of disease.	

Study	Design	Results
	• Early disability progression seems to be driven by inflammation, but later progression is associated with an ill-defined chronic neurodegenerative process, which is mostly unamenable to treatment with currently available therapies. • The goal of treatment is to minimize the accumulation of irreversible disability and, ultimately, to slow or stop disease progression, thus minimizing long-term disability and preserving a good quality of life. • Therefore, conventional treatment paradigms need to be reconsidered in patients with aggressive MS, so as to avoid late identification and subsequent treatment with aggressive treatments that offer too little too late. Specific treatments for aggressive MS • Summary of key treatments (prior to publication in 2015) • Treatment algorithm suggested	

The Canadian Journal of Neurological Sciences (2024), 1–4
doi:10.1017/cjn.2024.267

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Commentary

Health Canada Drug Approval Process: A Barrier to Personalized Care in Multiple Sclerosis

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Keywords: CADTH; health Canada; multiple sclerosis; prescribing practices; reimbursement

Introduction

Multiple sclerosis is a chronic neurological disorder characterized by inflammation, demyelination and axonal loss in the central nervous system (CNS). It is most commonly diagnosed in people aged 20–40 years and is associated with progressive neurodegeneration and disability during the lifelong course of the disease. Accumulating science in recent years suggests that MS is a disease continuum and that current subtypes of MS are insufficient to reflect underlying disease biology[1].

The first disease-modifying therapy (DMT) for MS was approved by Health Canada in 1995, and 18 DMTs have now received marketing authorization. All therapies target varying aspects of the dysregulated immune response in MS with significant differences in the relative efficacy of individual DMTs. Therapies considered to be of higher efficacy include oral agents that sequester T cells in secondary lymphoid organs (fingolimod, ozanimod, ponesimod, siponimod) or deplete T and B cells (cladribine); and monoclonal antibodies administered by infusion or injection that target B cells (ocrelizumab, ofatumumab) and T and B cells (alemtuzumab) or block lymphocyte entry into the CNS (natalizumab).

While the number of treatment options would appear to offer clinicians and persons with MS (PwMS) a plethora of choices, Health Canada's approach to approving drugs only for specific subtypes of MS and as first- or second-line therapy has imposed onerous restrictions on how clinicians may prescribe treatments necessary to improve clinical outcomes. Choices are further limited by government-mandated bodies such as the Canadian Agency for Drugs and Technologies in Health (CADTH) and the Institut national d'excellence en santé et services sociaux (INESSS), which evaluate and recommend how these medications should be used, as well as by provincial and private payors, who may further constrain prescribing based on the government's recommendations and seemingly arbitrary corporate policies.

The net result of this prescribing process might be termed Procrustean, named for the figure in Greek mythology who stretched or amputated his victims to fit the length of a bed. MS clinicians must force-fit PwMS into predetermined categories (e.g., MS phenotype, disease activity, age) to access DMTs and obtain reimbursement as the cost of most DMTs is prohibitive for most pwMS without reimbursement. The alternative for clinicians is to prescribe a suboptimal therapy until the PwMS worsens sufficiently to meet the criteria for a more effective treatment, which can often result in irreversible neurological disability accumulation, poor quality of life and long-term personal and professional consequences.

This issue, which is one of the greatest challenges encountered in MS clinical practice in Canada, was addressed at a meeting of an MS expert panel, held on September 29, 2023, in Toronto. The following outlines the group's discussions on how Health Canada's outdated process of drug approval infringes on current efforts to personalize and optimize care in pwMS and how such restrictions may contribute to suboptimal clinical outcomes.

Pathophysiology and clinical course of MS

The Lublin-Reingold classification scheme described several subtypes of MS, which were later consolidated into three clinical courses: relapsing-remitting (RRMS), in which acute attacks were

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Cite this article: Oh J, Bhan V, Traboulsee A, Morrow SA, Lee L, Levin M, Casserly C, Freedman MS, Giacomini PS, Émond F, Smyth P, Clift F, and Selchen D. Health Canada Drug Approval Process: A Barrier to Personalized Care in Multiple Sclerosis. *The Canadian Journal of Neurological Sciences*, https://doi.org/10.1017/cjn.2024.267

followed by periods of remission; primary-progressive (PPMS), characterized by gradual disability worsening from the outset; and secondary-progressive (SPMS), in which RRMS transitions to a progressive course[2]. These descriptions, based on clinical observations from a physician survey rather than from rigorous biological evidence, were intended primarily to standardize patient groups for epidemiologic studies and clinical trials.

The classification system subsequently added clinically isolated syndrome (CIS), a form of inflammatory demyelination not meeting the full diagnostic criteria for MS, as well as the phenotype modifiers of disease activity and progression. "Disease activity" referred to inflammatory activity (i.e., relapses and inflammatory lesions detected as new gadolinium-enhancing or new/enlarging lesions observed on T2-weighted sequences on magnetic resonance imaging [MRI]); this was intended as a means of identifying PwMS who were more likely to respond to a DMT, all of which target inflammation via various mechanisms. "Progression" referred to worsening neurological disability during relapse-free periods (now termed progression independent of relapse activity [PIRA]); by definition, progression was only considered in PwMS in progressive phases of the disease (SPMS, PPMS)[3].

These descriptions conformed to a two-stage hypothesis of MS, which posited that an initial inflammatory phase eventually progressed to a secondary neurodegenerative phase of the disease. However, it is now apparent that MS is a single disease entity in which inflammation and neurodegeneration co-occur from the earliest stages; indeed, evidence of neurodegeneration has been identified even before MS onset[4].

Key pathological features during the clinical course of MS are the development of peripheral immune activation, in which activated lymphocytes and monocytes enter the CNS and cause focal white-matter lesions; diffuse inflammation that is compartmentalized within the CNS and characterized by activation of macrophages/microglia and astrocytes; and demyelination and axonal loss resulting from innate and acquired immune activation, redistribution of sodium ion channels, accumulation of calcium ions and mitochondrial failure that damages neurons and impedes remyelination (reviewed in[1]). Patient-specific factors, such as genetics, environmental exposures and age, will influence the clinical expression of the disease. Thus, disability progression is not the result of a single disease mechanism. Rather, it is due to a combination of several mechanisms that act to varying degrees in individual PwMS throughout their clinical course, making current disease subtyping inadequately reflective of clinically relevant biological processes in pwMS.

Health Canada approval of MS treatments

Health Canada approvals of DMTs limit the use to specific disease phenotypes (RRMS, SPMS, PPMS); in some instances, inflammatory disease activity (relapses, MRI lesions) must be present. In addition, some treatments are designated as second-line agents, that is, after ≥1 prior treatment has been shown to produce an inadequate response or has been poorly tolerated.

Drug indications are ostensibly based on clinical trial data, although this evidence-based approach is applied inconsistently. For example, the phase III trials for all of the drugs approved as second-line agents (fingolimod, natalizumab, cladribine) primarily enrolled previously untreated PwMS. The only pivotal trial of second-line use was for alemtuzumab, which is indicated by Health Canada as a third-line agent.

Another example of the inconsistency of drug indications can be observed with the labeling for sphingosine 1-phosphate receptor (S1PR) modulators, a class of drugs that sequesters activated T cells in secondary lymphoid organs that has been found to be beneficial in pwMS. Two of these drugs (ozanimod, ponesimod) are indicated for any RRMS patient; one (fingolimod) is recommended in RRMS after prior treatment failure, and one (siponimod) is limited to active SPMS.

Such a regulatory approach contrasts with that adopted in 2019 by the US Food and Drug Administration (FDA), which permitted the approval of all higher-efficacy DMTs for a wide range of MS indications, specifically, the treatment of all relapsing forms of MS, which includes CIS, RRMS and active SPMS. Although this approach was welcomed by MS neurologists as it greatly simplified prescribing, it was not necessarily evidence-based. Most DMTs have not been studied in CIS and SPMS populations. However, the FDA likely adopted this approach as there is growing recognition of the need to revisit MS disease subtyping. The FDA does not designate DMTs as first- or second-line therapies; the sole exception is alemtuzumab, which is labeled as a third-line agent.

The limitations imposed by Health Canada's emphasis on phenotypes are further complicated by the heterogeneity of provincial and private payors with differing criteria for PwMS to access specific DMTs. An example is ocrelizumab, an anti-CD20 monoclonal antibody that depletes B cells, which is currently approved in Canada for RRMS and PPMS. In Quebec, the Régie de l'assurance maladie du Québec (RAMQ) specifies that it may only be prescribed in PwMS with an Expanded Disability Status Scale (EDSS) score <7.0 (the disability level when at least a wheelchair is required to ambulate short distances). In Ontario, the Exceptional Access Program requires an EDSS score <6.0 (the disability level when at least a unilateral walking aid is required to ambulate short distances). In British Columbia, the PharmCare program does not reimburse ocrelizumab in RRMS, opting to reimburse rituximab, another anti-CD20 agent that is not approved in Canada for the treatment of MS.

Evolution of MS research

Current drug authorizations and reimbursements support a stepwise approach in which a highly effective therapy is generally employed only after one or more treatment failures. This does not take into account how rapidly evolving MS research has led to new treatment strategies. It is now generally accepted that the benchmark of relapse activity is an inadequate indicator of long-term outcome, which has required the recognition of other determining factors. Progression that occurs during relapse-free periods, also known as PIRA, is now viewed as the main driver of accumulating disability, blurring the distinction between relapsing and progressive forms of the disease[5]. Accordingly, the new treatment paradigm is to use higher-efficacy therapy early in the disease course to limit the neurodegeneration that results in progression of disability.

The concept of progression itself is undergoing expansion to supplement the limitations of the EDSS by including additional indicators of disability worsening, such as those obtained with novel MRI techniques, neurocognitive testing and patient-reported outcomes. Numerous imaging, fluid and digital biomarkers now in development also have the potential to refine prognosis and more precisely monitor the therapeutic response of individual PwMS, further enabling clinicians and PwMS to personalize therapy based

https://doi.org/10.1017/cjn.2024.267 Published online by Cambridge University Press

on the individual's risk profile, underlying disease mechanisms and personal preferences.

Barriers to optimal treatment selection

In conforming to outdated models of MS pathophysiology, health regulators and provincial payors create a Procrustean prescribing environment: MS specialist neurologists are not free to select a drug that best meets the requirements of a given PwMS, but rather the PwMS must conform to the drug's labeling and reimbursement requirements. Common examples are when a newly diagnosed PwMS plans to become pregnant but cannot start with an intermittent therapy (e.g., cladribine, ocrelizumab, ofatumumab) that would allow for safe family planning without fetal exposure to a DMT or a PwMS with a rapidly evolving disease cannot receive a highly effective DMT (e.g., natalizumab); in both instances, these drugs are not considered first-line agents. PwMS with a worsening disability may not meet reimbursement criteria due to disability level (e.g., EDSS ≥6.0) or age (e.g., ≥55 years) despite the variability of an individual's disease and drug response. With siponimod, one of the few DMTs to demonstrate efficacy in SPMS, active disease must be demonstrated to access this DMT after the transition to SPMS – even if a prior treatment has effectively suppressed disease activity. Moreover, if treatment is ineffective, the PwMS, now recorded as having the SPMS phenotype in medical records so as to access siponimod, may no longer be eligible for another higher-efficacy treatment since the alternative options are indicated only for RRMS.

The path to personalized care in MS

The path to personalized care in MS is evolving from a focus on outdated disease phenotypes to a multifactorial approach that incorporates an assessment of the individual PwMS's pathobiology at different stages of their disease, genetic and environmental risks, physical and cognitive disability, comorbidities, life stage (including family planning) and patient-reported measures, such as symptomatology, quality of life and treatment satisfaction. Such assessments will become further refined with the ongoing advances in neuroimaging (MRI, positron emission tomography, optical coherence tomography), fluid biomarkers (including neurofilament-light chain, a marker of neuronal damage and glial fibrillary acidic protein, a marker of astrocyte activation, among others) and digital biomarkers (e.g., for gait analysis, eye tracking, wearable devices).

As these technologies become the new standard of care, regulators may consider adding additional criteria utilizing these new biomarkers before a treatment will be reimbursed. However, this would only further complicate access to necessary DMTs and lose sight of the overall goal: to employ a treatment that will optimally control an individual PwMS's disease to improve long-term outcomes. Achieving this goal would necessitate clinicians having a freer hand in prescribing so as to develop a personalized treatment regimen that may often include new/emerging DMTs according to their best clinical judgment. In MS, clinical and research data are constantly expanding and evolving, and arguably only a neurologist with expertise in MS has the knowledge and experience to interpret the many sources of clinical, imaging and laboratory data to make an informed decision about an individual PwMS. This same complexity of decision-making would likely require that DMT prescribing be limited to MS neurologists at MS clinics and community neurologists with expertise in MS, a situation that already exists in several Canadian provinces. MS clinics would need to expand community outreach programs (which might include virtual care options) and increase fellowship training and preceptorship programs to ensure equitable access to DMTs in rural and other underserved communities.

Cost considerations

Higher-efficacy DMTs are generally more costly than first-line oral and injectable therapies. However, enabling neurologists with expertise in MS and PwMS to have greater access to these medications, notably as first-choice agents, would be expected to reduce the overall cost of MS care over the disease course, which spans decades. Many PwMS on a higher-efficacy DMT remain relapse-free, which could translate to considerable savings on this measure alone. The Canadian Prospective Cohort Study to Understand Progression in Multiple Sclerosis (CanProCo) estimated that the annual excess cost of one relapse requiring hospitalization was CDN$10,543 per patient[6]. Similarly, a US cost-effectiveness analysis comparing ocrelizumab with a modest-efficacy injectable beta-interferon found that improved disease control was associated with substantial savings relating to relapse prevention, drug monitoring and adverse event-related costs[7].

There would be additional economic benefits associated with the judicious use of higher-efficacy DMTs according to the MS specialist's clinical judgment. Head-to-head trials have demonstrated that high-efficacy DMTs outperform modest-efficacy agents in reducing short- and long-term disability and slowing the rate of brain volume loss[8–10]. Improved care would lower costs associated with worsening disability, such as hospitalizations, physician visits and symptomatic medications, and reduce the economic cost of MS on a societal level related to employment disability. A recent Canadian study demonstrated that even in the earliest stages of MS, there is a substantial loss of workplace productivity, and allowing pwMS to have access to DMTs that minimize disability accrual over time has the potential to substantially reduce MS-related disability that may eventually result in the inability to remain employed[11]. While payors' drug budgets tend to focus narrowly on drug costs rather than overall savings to the health care system ("siloing"), it is noteworthy that drug acquisition costs were lower for ocrelizumab versus beta-interferon in the above-cited US study, although it should be noted that drug pricing differs in the USA.

MS care is a rapidly changing therapeutic environment requiring complex decision-making to optimize treatment based on the needs of the individual PwMS as they evolve during the clinical course. The goal of personalized medicine cannot be achieved if neurologists with expertise in MS do not have the freedom to act in the best interest of PwMS due to the inflexible restrictions imposed by regulators and payors. We believe it is time for regulators – starting with Health Canada – and payors to consider these points for current and future DMT approvals and indications so that clinical outcomes can be maximized for PwMS in Canada and beyond.

Acknowledgments. The authors acknowledge the editorial assistance of Steven Manners of Communications Lansdowne, whose help was made possible through funding from EMD Serono Canada.

Author contributions. All of the authors contributed to the discussions, reviewed all drafts and approved the final version of this manuscript. Authors did not receive any remuneration for their meeting attendance or review of the manuscript.

https://doi.org/10.1017/cjn.2024.267 Published online by Cambridge University Press

Funding statement. Funding was provided by EMD Serono Canada for editorial and travel assistance and article processing charges. EMD Serono Canada was not involved in the drafting or review of the manuscript at any stage of the process and had no input in the content of the manuscript. Authors received no remuneration for their work in writing, editing or reviewing the manuscript.

Competing interests. **Dr Jiwon Oh** has received institutional grants from Biogen Idec and Hoffmann-La Roche; consulting fees from EMD Serono, Biogen Idec, Sanofi-Genzyme, Novartis, Horizon Therapeutics, Eli-Lilly and Hoffmann-La Roche; and financial support for attending meetings from EMD Serono, Sanofi-Genzyme and Hoffmann-La Roche, is Chair of the Medical Advisory Committee of MS Canada and holds the Waugh Family Chair in MS Research at St Michael's Hospital, University of Toronto.

Dr Virender Bhan has received honoraria from Sanofi Canada and EMD Serono and financial support for attending meetings from EMD Serono and has participated in advisory boards for Novartis.

Dr Anthony Traboulsee has received institutional grants from Sanofi and Hoffmann-La Roche and consulting fees from Sanofi and Hoffmann-La Roche and has participated in advisory boards for Sanofi.

Dr Sarah Morrow has received grants from EMD Serono, Hoffmann-La Roche, Novartis, Bristol Myers Squibb/Celgene and Sanofi-Genzyme; consulting fees from Biogen Idec, Sanofi-Genzyme, EMD Serono, Amgen, Novartis and Hoffmann-La Roche; honoraria from Biogen Idec, EMD Serono and Novartis; and funding from the Consortium of Multiple Sclerosis Centers, MS Canada and the Canadian Network of MS Clinics.

Dr Liesly Lee has received grants from Hoffmann-La Roche, Sanofi and Novartis and participated in advisory boards for Novartis and Hoffmann-La Roche and in staff preceptorship programs for Novartis.

Dr Michael Levin has received grants from the MS Canada Saskatchewan Health Research Foundation, Consortium of MS Centers Saskatoon City Hospital Foundation and the Tri-Agency New Frontiers in Research Fund; honoraria from Biogen, Novartis, the Merck Manual and EMD Serono; and support for attending meetings from EMD Serono and holds a patent for a potential therapy for neurodegenerative disorders.

Dr Courtney Casserly has received a Western Libraries Open Access Medical Education Grant, a Teaching Innovation Award from Western University and a grant from Biogen Idec; consulting fees from Amgen, Novartis, EMD Serono, Biogen Idec, Hoffmann-La Roche, Horizon Therapeutics, Sanofi-Genzyme and Alexion; and a travel grant from the Ontario Medical Association.

Dr Mark S. Freedman has received grants from Sanofi-Genzyme and consulting fees and honoraria from Alexion/AstraZeneca, Biogen Idec, EMD Inc./EMD Serono/Merck Serono, Find Therapeutics, Hoffmann-La Roche, Horizon Therapeutics/Amgen, Novartis/Sandoz, Sanofi-Genzyme, Sentrex and Teva Canada Innovation and has participated in advisory boards for Alexion/AstraZeneca, Neurogenesis, Actelion/Janssen (J&J), Novartis, Atara Biotherapeutics, Bayer Healthcare, Sanofi-Genzyme, Celestra Health, Sentrex, EMD Inc./Merck Serono, Setpoint Medical and Hoffmann-La Roche.

Dr Paul S. Giacomini has received grants from EMD Serono, Sanofi-Genzyme and Hoffmann-La Roche; consulting fees and/or honoraria from Innodem Neurosciences, Novartis, Hoffmann-La Roche, EMD Serono, Biogen, Sanofi-Genzyme, Amgen/Horizon Therapeutics and Teva Neuroscience; and support for attending meetings from Hoffmann-La Roche, Sanofi-Genzyme and EMD Serono and is an employee of Innodem Neurosciences and holds stock options.

Dr François Émond has received grants from EMD Serono, Novartis and Sanofi and honoraria from Bristol Myers Squibb, Biogen Idec, EMD Serono and Novartis and has participated in advisory boards for EMD Serono, Novartis and Biogen Idec.

Dr Penelope Smyth has received consulting fees and/or honoraria from Novartis, Hoffmann-La Roche, Biogen Idec and EMD Serono, serves as an Advisory Committee member for MS Canada and is the president of the Canadian Network of MS Clinics.

Dr Fraser Clift has received consulting fees and honoraria from Biogen, EMD Serono, Novartis, Hoffmann-La Roche, Alexion, Sanofi and Bristol Myers Squibb and financial support for attending meetings from Biogen, EMD Serono, Novartis and Sanofi and has participated in advisory boards for Biogen, EMD Serono, Novartis, Hoffmann-La Roche, Alexion, Sanofi and Bristol Myers Squibb.

Dr Daniel Selchen has received honoraria from Biogen, Bristol Myers Squibb, EMD Serono, Novartis, Pfizer, Hoffmann-La Roche and Sanofi and payment for expert testimony from Teva and has participated in advisory boards for EMD Serono, Novartis, Hoffmann-La Roche and Sanofi.

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https://doi.org/10.1017/cjn.2024.267 Published online by Cambridge University Press

Stakeholder Feedback Submission - Proposed Project Scope

CDA-AMC Reimbursement Review Project Number: TS0004-000

Cladribine and natalizumab for highly active relapsing-remitting multiple sclerosis

https://www.cda-amc.ca/cladribine-and-natalizumab-highly-active-relapsing-remitting-multiple-sclerosis

Questions #1: Do you think that the project as proposed in the project scope document will be useful to those making policy or clinical practice decisions? Why or why not?

Yes, we agree that the proposed project would be useful in decision-making. However, we have noticed that the proposed Scope does not discuss how CDA-AMC will define highly active MS in their review. In the previous CDA-AMC Health Technology Review (Project Number: HT0030-000)[1], it was mentioned that "There was no prespecified definition for highly active RRMS, to avoid excluding potentially relevant evidence." We agree that highly active RRMS should be identified based on these 4 domains: relapse frequency, relapse severity, relapse recovery, and key lesions on brain scan[2]. It would be important that timely recommendations are made with this review considering the already comprehensive review conducted by CDA-AMC previously (Project Number: HT0030-000).

Natalizumab treatment has been shown to be highly effective against disability progression and relapse in comparison with placebo, including patients with highly active disease and with a rapid and sustained beneficial effect[3,4,5]. For MS patients who are at risk of an aggressive clinical course, worse outcomes, and/or a poorer response to DMT, (e.g. males, individuals of non-White ethnicity, and those with high-risk clinical/radiological disease factors – natalizumab is a particularly suitable option for such patients given its rapidity of response in preventing the development of lesions and reducing ARR[4, 6].

For reasons mentioned above, natalizumab has been recommended as a treatment option for highly active RRMS patients by a group of Canadian MS experts[7].

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Questions #2: Are there policy, practice or research questions not considered in the project scope that are required to change or influence practice? If so, what would these be?

Tysabri (natalizumab) received notice of compliance (NoC) from Health Canada in September 2006, and Mavenclad (cladribine) received NoC in November 2017[1]. Consider the timing of when pivotal RCTs were conducted, we would like to highlight the limitations of comparative efficacy research, with few studies and no RCT comparing natalizumab and cladribine as first-line treatments in patients with highly active RRMS to drugs currently used as front-line treatment. Recommend expanding the Study Design to also include real world data. Please refer to studies suggested in Questions #1, #3 and #4.

References:

1) Health Canada NOC Database, https://health-products.canada.ca/noc-ac

Questions #3: Do you have any suggestions for improving the project as proposed in the project scope document?

Consider inclusion of two additional endpoints which are especially relevant to patients with highly active MS.

1)**"No Evidence of Disease Activity" (NEDA)** is a composite endpoint demonstrating broad freedom from disease activity, an outcome that has become possible thanks to "high-efficacy" DMTs.

2) **Onset of action** is an endpoint that has become particularly relevant with increasing disease activity, as quicker relief from debilitating symptoms and disability, is highly desirable.

Biogen requests that CDA-AMC further expand the acceptable methodologies of studies which may be reviewed. We would like to commend CADTH's current Scope for accepting non-RCT data to some extent, in the form of comparative prospective cohort studies. However, we hope that CADTH will consider expanding this to include non-comparative, prospective long-term studies. If not, CDA-AMC's review will miss out on multiple rich long-term studies on safety and durability of efficacy, which would make this review extremely challenging to conduct a comparative analysis. For example, a published 10-year analysis of observational data from the Tysabri Observational Program (TOP) offers a robust prospective analysis of long-term safety and effectiveness of natalizumab in thousands of patients with MS[1]. Real-world data can provide clinicians and patients practical benefit-risk information when

considering treatment options. The TOP analysis began over 15 years ago, is the largest real-world study of natalizumab-treatment patients with RRMS[2].

References:

1) Butzkueven H, Kappos L, Wiendl H, et al. J Neurol Neurosurg Psychiatry. 2020;91(6):660-668. doi:10.1136/jnnp-2019-322326
2) Trojano M et al. Presented at 9th EAN Congress 2023: July 1-4 2023 EPO- 658

Questions #4: Please provide any additional comments you may have about this document or the project itself, including any studies you think should be included in our review.

Key Natalizumab Trials for Consideration for CDA-AMC Highly Active First Line Project

Phase III Randomized Trial (AFFIRM/SENTINEL)

- In AFFIRM, a patient population is >90% treatment naïve, natalizumab significantly reduced the progression of disability, the occurrence of clinical relapse, and MRI lesions; authors suggested the results indicate it could offer greater benefit than other therapies available
- Efficacy is realized early and persists throughout the treatment period.
- Highly Active subgroup patients defined as ≥ 2 disabling relapses in 1 year prior to study entry and ≥ 1 gadolinium enhancing (Gd+) lesions
    - Natalizumab reduced the risk of 24-week confirmed disability progression and relapse rate in treatment-naïve patients with highly active disease by 64% and by 81%, respectively.
    - The proportion of patients with no evidence of disease activity (NEDA) over 2 years was significantly greater in the natalizumab group than in the placebo group (27.4% versus 1.7%; 95% confidence interval [CI], 17.7 33.7%, p < 0.0001). A greater proportion of patients with highly active disease had NEDA in the second year than in the first year of natalizumab treatment.
    - A difference in the cumulative probability of relapse from baseline between the natalizumab and placebo groups was first observed at day 45 in patients with highly active disease, 6.8% for natalizumab and 16.6% for placebo (HR: 0.35; 95 % CI, 0.14 – 0.87; p = 0.0243).
    - Statistically significant effects were observed in the probability of confirmed disability improvement over 2 years and the drug's effect on quality-of-life (QoL) measures vs placebo.
- AFFIRM study and its sub-analyses were pivotal in regulatory submissions to the European Medicines Agency (EMA) in gaining a label for natalizumab use in patients with highly active MS.

References:

Polman, C. et al. N Engl J Med 2006;354:899-910
Hutchinson M, Kappos L, Calabresi PA, et al.. J Neurol. 2009;256(3):405-15.

Havrdova E, Galetta S, Hutchinson M, et al. Lancet Neurol. 2009;8(3):254-60.

Phillips JT, Giovannoni G, Lublin FD, et al.. Mult Scler. 2011;17(8):970-9.

Kappos L, O'Connor PW, Polman CH, et al.. J Neurol. 2013;260(5):1388-95.

Kieseier B, Putzki N, Bates D, et al. Presented at: 19th Meeting of the European Neurological Society (ENS); Jun 20, 2009; Milan; Italy. Poster P351.

Ph II – MRI Outcomes (weight based dosing of natalizumab vs placebo)

- Patient population aligns to a highly active cohort (mean relapses in previous 2 years was 3, ~40% had Gd lesions)
- Significant reduction in mean number of new lesions in both natalizumab groups vs placebo
- Rapid onset: effect was evident one month after the first infusion and was sustained throughout the treatment period
- Improvements in well-being scores for natalizumab patients

References:
Miller N Engl J Med 2003;348:15-23.

Other observational data from high quality sources

Tysabri Observational Program (TOP) Analyses

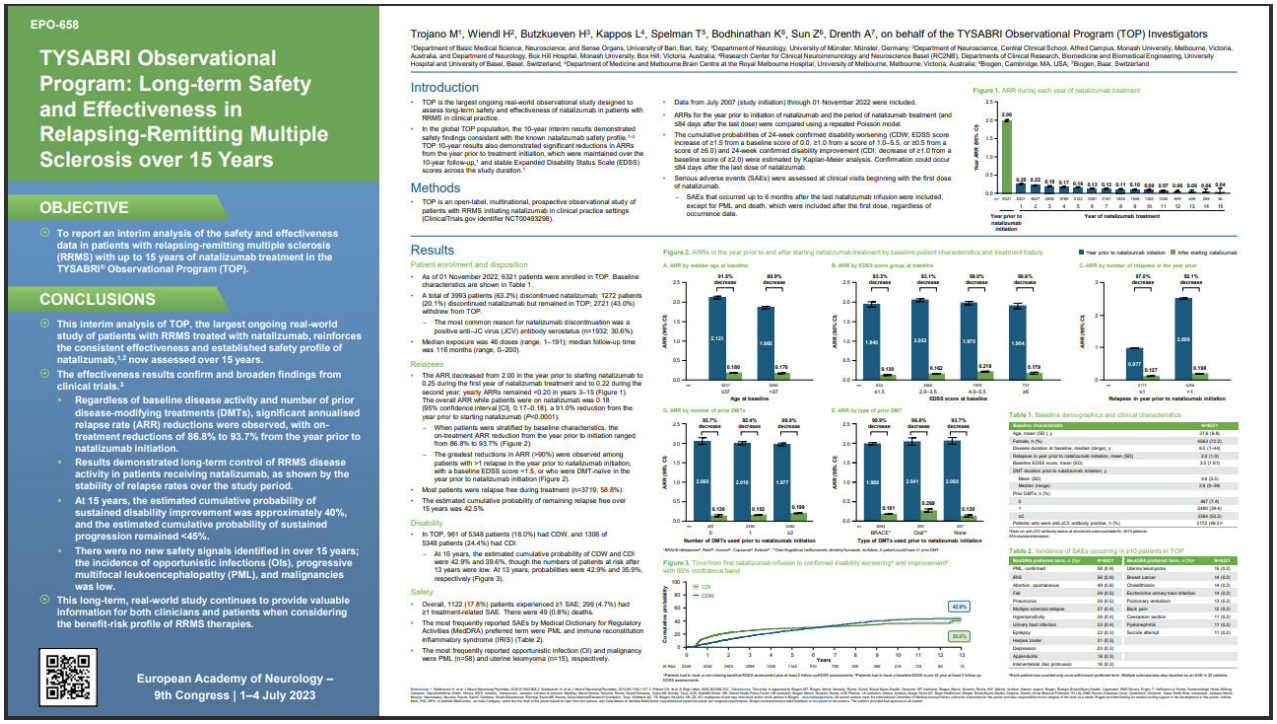
- TOP is the largest ongoing real-world observational study designed to assess long-term safety and effectiveness of natalizumab in patients with RRMS in clinical practice.
- During the 10 years of follow-up, the on-natalizumab ARR was 0.15 (95% CI 0.14 to 0.15), a 92.5% reduction from the ARR of 1.99 (95% CI 1.97 to 2.02) in the year prior to starting natalizumab (overall aligned with active group, mean relapses in year prior=2). Patients had large reductions across subgroups including those with 0 prior DMTs.
- Cumulative probability disability improvement in treatment naïve subgroup (aligned with highly active characteristics: >80% had Gd lesions, relapses in year prior >2) up to 47.9%
- In TOP patients with a median (range) baseline EDSS score of 3.5 (0.0–9.5) and mean relapses in year prior of 2.01, who completed 24 months of natalizumab treatment, the rate of 48-week confirmed disability worsening events was below 15%; after approximately 5.5 years of natalizumab treatment, 86.5% and 94.7% of patients did not have EDSS score increases of ≥1.0 or ≥2.0 points, respectively

References:
Butzkueven H, Kappos L, Wiendl H, et al. J Neurol Neurosurg Psychiatry. 2020;91(6):660-668. doi:10.1136/jnnp-2019-322326

Trojano M, Butzkueven H, Kappos L, et al.. Mult Scler Relat Disord. 2018;24:11-19. doi:10.1016/j.msard.2018.04.020

Wiendl H, Spelman T, Butzkueven H, et al. Mult Scler. 2021;27(5):719-728. doi:10.1177/1352458520926869

The interim analysis of the safety and effectiveness data in patients with RRMS with up to **15 years** of natalizumab treatment in TOP was presented at the European Academy of Neurology Congress in July 2023. This long-term, real-world study continues to provide valuable information for both clinicians and patients when considering the benefit-risk profile of RRMS therapies.



EPO-658

TYSABRI Observational Program: Long-term Safety and Effectiveness in Relapsing-Remitting Multiple Sclerosis over 15 Years

OBJECTIVE

- To report an interim analysis of the safety and effectiveness data in patients with relapsing-remitting multiple sclerosis (RRMS) with up to 15 years of natalizumab treatment in the TYSABRI® Observational Program (TOP).

CONCLUSIONS

- This interim analysis of TOP, the largest ongoing real-world study of patients with RRMS treated with natalizumab, reinforces the consistent effectiveness and established safety profile of natalizumab,[1,2] now assessed over 15 years.
- The effectiveness results confirm and broaden findings from clinical trials.[3]
  - Regardless of baseline disease activity and number of prior disease-modifying treatments (DMTs), significant annualised relapse rate (ARR) reductions were observed, with on-treatment reductions of 86.8% to 93.7% from the year prior to natalizumab initiation.
  - Results demonstrated long-term control of RRMS disease activity in patients receiving natalizumab, as shown by the stability of relapse rates over the study period.
  - At 15 years, the estimated cumulative probability of sustained disability improvement was approximately 40%, and the estimated cumulative probability of sustained progression remained <45%.
  - There were no new safety signals identified in over 15 years; the incidence of opportunistic infections (OIs), progressive multifocal leukoencephalopathy (PML), and malignancies was low.
- This long-term, real-world study continues to provide valuable information for both clinicians and patients when considering the benefit-risk profile of RRMS therapies.

European Academy of Neurology – 9th Congress | 1–4 July 2023

Trojano M[1], Wiendl H[2], Butzkueven H[3], Kappos L[4], Spelman T[5], Bodhinathan K[6], Sun Z[6], Drenth A[7], on behalf of the TYSABRI Observational Program (TOP) Investigators

[1]Department of Basic Medical Science, Neuroscience, and Sense Organs, University of Bari, Bari, Italy; [2]Department of Neurology, University of Münster, Münster, Germany; [3]Department of Neuroscience, Central Clinical School, Alfred Campus, Monash University, Melbourne, Victoria, Australia, and Department of Neurology, Box Hill Hospital, Monash University, Box Hill, Victoria, Australia; [4]Research Center for Clinical Neuroimmunology and Neuroscience Basel (RCNB), Departments of Clinical Research, Biomedicine and Biomedical Engineering, University Hospital and University of Basel, Basel, Switzerland; [5]Department of Medicine and Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Melbourne, Victoria, Australia; [6]Biogen, Cambridge, MA, USA; [7]Biogen, Baar, Switzerland

Introduction

- TOP is the largest ongoing real-world observational study designed to assess long-term safety and effectiveness of natalizumab in patients with RRMS in clinical practice.
- In the global TOP population, the 10-year interim results demonstrated safety findings consistent with the known natalizumab safety profile.[1,2] TOP 10-year results also demonstrated significant reductions in ARRs from the year prior to treatment initiation, which were maintained over the 10-year follow-up,[1] and stable Expanded Disability Status Scale (EDSS) scores across the study duration.[1]

Methods

- TOP is an open-label, multinational, prospective observational study of patients with RRMS initiating natalizumab in clinical practice settings (ClinicalTrials.gov identifier NCT00493298).
- Data from July 2007 (study initiation) through 01 November 2022 were included.
- ARRs for the year prior to initiation of natalizumab and the period of natalizumab treatment (and ≤84 days after the last dose) were compared using a repeated Poisson model.
- The cumulative probabilities of 24-week confirmed disability worsening (CDW; EDSS score increase of ≥1.5 from a baseline score of 0.0, ≥1.0 from a score of 1.0–5.5, or ≥0.5 from a score of ≥6.0) and 24-week confirmed disability improvement (CDI; decrease of ≥1.0 from a baseline score of ≥2.0) were estimated by Kaplan-Meier analysis. Confirmation could occur ≤84 days after the last dose of natalizumab.
- Serious adverse events (SAEs) were assessed at clinical visits beginning with the first dose of natalizumab.
  - SAEs that occurred up to 6 months after the last natalizumab infusion were included, except for PML and death, which were included after the first dose, regardless of occurrence date.

Figure 1. ARR during each year of natalizumab treatment

Results

Patient enrollment and disposition

- As of 01 November 2022, 6321 patients were enrolled in TOP. Baseline characteristics are shown in Table 1.
- A total of 3993 patients (63.2%) discontinued natalizumab; 1272 patients (20.1%) discontinued natalizumab but remained in TOP; 2721 (43.0%) withdrew from TOP.
  - The most common reason for natalizumab discontinuation was a positive anti–JC virus (JCV) antibody serostatus (n=1932; 30.6%).
- Median exposure was 46 doses (range, 1–191); median follow-up time was 116 months (range, 0–200).

Relapses

- The ARR decreased from 2.00 in the year prior to starting natalizumab to 0.25 during the first year of natalizumab treatment and to 0.22 during the second year; yearly ARRs remained <0.20 in years 3–15 (Figure 1). The overall ARR while patients were on natalizumab was 0.16 (95% confidence interval [CI], 0.17–0.18), a 91.0% reduction from the year prior to starting natalizumab (P<0.0001).
  - When patients were stratified by baseline characteristics, the on-treatment ARR reduction from the year prior to initiation ranged from 86.8% to 93.7% (Figure 2).
  - The greatest reductions in ARR (>90%) were observed among patients with >1 relapse in the year prior to natalizumab initiation, with a baseline EDSS score <1.5, or who were DMT-naïve in the year prior to natalizumab initiation (Figure 2).
- Most patients were relapse free during treatment (n=3719; 58.8%).
- The estimated cumulative probability of remaining relapse free over 15 years was 42.5%.

Figure 2. ARRs in the year prior to and after starting natalizumab treatment by baseline patient characteristics and treatment history

Disability

- In TOP, 961 of 5348 patients (18.0%) had CDW, and 1306 of 5348 patients (24.4%) had CDI.
  - At 15 years, the estimated cumulative probability of CDW and CDI were 42.9% and 39.6%, though the numbers of patients at risk after 13 years were low. At 13 years, probabilities were 42.9% and 35.9%, respectively (Figure 3).

Figure 3. Time from first natalizumab infusion to confirmed disability worsening* and improvement† with 95% confidence band

Safety

- Overall, 1122 (17.8%) patients experienced ≥1 SAE; 299 (4.7%) had ≥1 treatment-related SAE. There were 49 (0.8%) deaths.
- The most frequently reported SAEs by Medical Dictionary for Regulatory Activities (MedDRA) preferred term were PML and immune reconstitution inflammatory syndrome (IRIS) (Table 2).
- The most frequently reported opportunistic infection (OI) and malignancy were PML (n=58) and uterine leiomyoma (n=15), respectively.

Table 1. Baseline demographics and clinical characteristics

Table 2. Incidence of SAEs occurring in ≥10 patients in TOP

Reference:

Trojano M et al. Presented at 9th EAN Congress 2023: July 1-4 2023 EPO- 658

Spelman Neurol Clin Pract 2016;6:1–14

- Retrospective analysis; propensity matched from robust registries (TOP, MSBase)
- First-line natalizumab for RRMS improves relapse rates compared to first-line IFN-b/GA in higher disease groups

Lastly, there is a mistake in Table 1 – products available in Canada. There is currently no cladribine generics in oral formulation for the treatment of MS.

September 10, 2024

2695 North Sheridan Way, Mississauga, ON L5K 2N6, Canada

September 13, 2024

Canada's Drug Agency - Reimbursement Review
Cladribine and Natalizumab for Highly Active Relapsing-Remitting Multiple Sclerosis
Project TS0004

Feedback to the Proposed Scope (Cladribine and Natalizumab for Highly Active Relapsing-Remitting Multiple Sclerosis - TS0004)

EMD Serono appreciates the opportunity to provide feedback on this streamlined review, specifically regarding the review of MAVENCLAD (cladribine) for use as first-line treatment in patients with highly active relapsing multiple sclerosis (RRMS). We commend CDA's inclusion of patient and physician groups in this review. Serious consideration of their perspective and expert advice will result in a more impactful recommendation by the Formulary Management Expert Committee (FMEC).

Regrettably, findings from the previous CADTH Health Technology Review (May 2024) could not be translated into listing criteria for public drug plan implementation. However, we are reassured that the CDA will leverage this report and therefore would anticipate for the revised final recommendation to be issued in less than the typical 4 to 6-month timeframe, in accordance with the Procedures for CDA-AMC Streamlined Reviews. In the absence of new significant clinical evidence, we urge that the FMEC proceeds without further delay to the Recommendation Phase.

Product characteristics of cladribine for RRMS

Cladribine (Mavenclad, ~~generics~~)	EMD Serano	Oral	Adenosine nucleoside analog	Moderate-high

Cladribine tablets, manufactured by EMD Serono and sold under the brand name MAVENCLAD®, does not have generic alternatives approved in Canada.

EMD Inc., Canada
200-2695 North Sheridan Way
Mississauga, ON L5K 2N6
Tel: + (1) [redacted]

Dosing considerations

Interventions	Cladribine 3.5mg/kg orally over 2 years, administered as 1 treatment course of 1.75mg/kg per year Natalizumab 300mg IV infusion every 4 weeks

The recommended cumulative dose of MAVENCLAD is 3.5 mg/kg body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year, **followed by observation for another 2 years.**[1] The effective clinical response beyond the first 2 years for a majority of patients treated with cladribine has been demonstrated.[2,3,4] From an economic perspective, the annual drug acquisition cost of cladribine should therefore be averaged over a period of 4 years.

Thank you for your consideration of the above feedback, we look forward to participating in the next phase of the review.

References

1. Mavenclad (cladribine): 10 mg tablet [product monograph]. Mississauga (ON): EMD Serono; 2017 Nov 29: https://pdf.hres.ca/dpd_pm/00042413.PDF.
2. Giovannoni G, Soelberg Sorensen P, Cook S, et al. Safety and efficacy of cladribine tablets in patients with relapsing–remitting multiple sclerosis: Results from the randomized extension trial of the CLARITY study. Multiple Sclerosis Journal. 2018;24(12):1594-1604. doi:10.1177/1352458517727603
3. Meuth, S. G., Bayas, A., Kallmann, B., Linker, R., Rieckmann, P., Wattjes, M. P., … Kleinschnitz, C. (2022). Long-term management of multiple sclerosis patients treated with cladribine tablets beyond year 4. Expert Opinion on Pharmacotherapy, 23(13), 1503–1510. https://doi.org/10.1080/14656566.2022.2106783
4. Patti F, Visconti A, Capacchione A, Roy S, Trojano M. Long-term effectiveness in patients previously treated with cladribine tablets: a real-world analysis of the Italian multiple sclerosis registry (CLARINET-MS). Therapeutic Advances in Neurological Disorders. 2020;13. doi:10.1177/1756286420922685