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

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Drugs Health Technologies Health Systems

Reimbursement Review

Natalizumab and Cladribine

Requester: Public drug programs
Therapeutic area: Relapsing-remitting multiple sclerosis

Key Messages

What Is Relapsing-Remitting Multiple Sclerosis?

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

What Are the Treatment Goals and Current Treatment Options for RRMS?

MS remains an incurable disorder. The most important goal of therapy is prevention of neurological disability. Effective disease-modifying treatment (DMT) can delay the occurrence of disease complications and the development of disability.

Optimal sequencing of DMTs for RRMS treatment remains uncertain and includes considerations of efficacy, safety, and cost. In the classical approach, the escalating strategy relies on starting with DMTs with lower cost and more favourable safety profiles, despite low to moderate efficacy, and when disease activity is detected, treatment is upscaled to higher-efficacy DMTs. Another strategy is the early intensive strategy, which consists of starting with high-efficacy DMTs as first-line treatment even though they may have less favourable safety and cost profiles.

What Are Natalizumab and Cladribine and Why Did We Conduct This Review?

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

Evidence from the past 10 years supports moving to the early intensive treatment approach, with several observational studies showing better outcomes for patients who receive early treatment with high-efficacy DMTs. There are 2 high-efficacy DMTs currently reimbursed as first-line treatment of RRMS: ocrelizumab and ofatumumab. However, both clinicians who treat MS and patients living with the disease have expressed a need for more treatment options for the first-line treatment of RRMS that have different mechanisms of action and modes of administration for patients with different treatment needs.

Key Messages

How Did We Evaluate Natalizumab and Cladribine?

There are currently no published clinical trials directly comparing natalizumab or cladribine with other high-efficacy DMTs for RRMS. A recently published indirect treatment comparison — a network meta-analysis (also called a *mixed treatment comparison*) — was used to provide the most up-to-date evidence that simultaneously compared natalizumab and cladribine with other treatments for RRMS. Extensive input provided by clinicians and patients was also considered.

What Did We Find?

Clinical Evidence

The network meta-analysis showed that natalizumab and cladribine are more effective than all but 1 of the lower-efficacy DMTs of interest in reducing the frequency of relapses over 2 years of treatment. There was no difference between treatment with natalizumab or cladribine with other select treatment comparators, including 2 high-efficacy DMTs, regarding the number of people who experienced serious adverse events or discontinued treatment due to adverse events.

Economic Evidence

Based on public list prices, cladribine and natalizumab are expected to be associated with a per patient cost of $44,968 and $46,750 per year, respectively. Comparator costs for first-line treatments ranged from $5,449 (teriflunomide) to $48,867 (peginterferon beta-1a) per year. Therefore, cladribine was more costly than glatiramer acetate, interferon beta-1a, interferon beta-1b, ofatumumab, ocrelizumab, and teriflunomide, with incremental costs ranging from $12,368 (versus ocrelizumab) to $39,519 (versus teriflunomide) per patient annually. When compared to peginterferon beta-1a, cladribine resulted in cost-savings of $3,899 per patient per year. Natalizumab was more costly than glatiramer acetate, interferon beta-1a, interferon beta-1b, ofatumumab, ocrelizumab, and teriflunomide, with incremental costs ranging from $14,150 (versus ocrelizumab) to $41,301 (versus teriflunomide) per patient annually. Compared with peginterferon beta-1a, natalizumab showed cost-savings of $2,116 per patient per year. As such, the reimbursement of cladribine and natalizumab is generally expected to increase overall drug acquisition costs compared with currently reimbursed first-line RRMS treatments.

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Abbreviations

AE	adverse event
CDA-AMC	Canada’s Drug Agency
CI	confidence interval
CMSWG	Canadian MS Working Group
CNMSC	Canadian Network of Multiple Sclerosis Clinics
CNS	central nervous system
DMT	disease-modifying treatment
HRQoL	health-related quality of life
HTA	health technology assessment
MS	multiple sclerosis
OR	odds ratio
PML	progressive multifocal leukoencephalopathy
RCT	randomized controlled trial
RR	risk ratio
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event

Background and Review Methods

Disease

Multiple sclerosis (MS) is a chronic autoimmune-mediated inflammatory disease of the central nervous system (CNS) and is the most common progressive neurological condition of young adults.[1] It affects approximately 2.8 million people worldwide, with a high burden for patients and their caregivers and a substantial societal economic impact.[2] Canada has one of the highest rates of MS in the world, with an estimated 90,000 people living with the disease.[3] MS is most often diagnosed in adults aged 20 to 49 years; 60% of adults diagnosed with MS are between the ages of 20 and 49 years.[3] In Canada, the average age at time of MS diagnosis is 43 years.[3] Women are 3 times more likely to be diagnosed with MS than men; in Canada, 75% of people living with MS are women.[3]

The disease attacks myelin, the protective covering of the of nerve fibres. The demyelination of central nerve fibres disrupts the normal flow of electrical impulses along the nerves. Myelin damage can also lead to deterioration of the exposed nerves, resulting in irreversible damage to them. Tissue damage in MS results from a complex and dynamic interaction between the immune system, glia, and neurons. The inflammatory response leads to demyelination and early neuronal transection and a neurodegenerative process characterized by more diffuse inflammation later in the course of the disease.[4] The inflammatory and neurodegenerative processes can occur in parallel leading to progressively more disabling symptoms over time. Most often, MS is characterized by reversible episodes of neurological dysfunction, which is often followed by irreversible clinical disability. MS is a highly heterogenous disease in terms of clinical presentation. The most common symptoms include numbness or weakness in limbs, fatigue, visual disturbances, difficulty with coordination and balance, muscle spasm or stiffness, cognitive changes or memory problems, and difficulty speaking and swallowing.

Diagnosis of MS relies on clinical, imaging, and laboratory findings. The long-standing McDonald criteria are used for diagnosing MS; the 2017 revision of the McDonald criteria has facilitated an earlier and more accurate diagnosis of MS. The Canadian MS Working Group (CMSWG) recommends the use of these criteria for patients presenting clinically with events that are considered highly suspicious for CNS demyelination after exclusion of reasonable alternative diagnoses.[5] The 2017 McDonald criteria enable more patients experiencing a first clinical event to be diagnosed with MS with greater sensitivity but with lower specificity. The diagnostic criteria require evidence of damage in at least 2 separate areas of the CNS to confirm dissemination in space, evidence that confirms dissemination in time (which can be done at a single time point of onset), and ruling out other possible causes. In addition, imaging evidence and cerebrospinal fluid findings should be consistent with demyelinating disease.[6]

Four major MS disease phenotypes are traditionally recognized: clinically isolated syndrome, relapsing-remitting MS (RRMS), secondary progressive MS, and primary progressive MS.[7] Most people who develop MS are initially diagnosed with RRMS, characterized by discrete episodes of neurological impairment or exacerbation of symptoms (called *relapses*) that have an acute and unpredictable onset, followed by periods of stability or improvement (called *remissions*). The nerves that are affected, the severity of attacks, the degree of recovery, and the time between relapses all vary widely from person to person. The relapse rate

and degree of recovery after a relapse predict long-term disability.[8] In Canada, approximately 90% of people living with MS are initially diagnosed with RRMS.[7] There is a subgroup of patients with RRMS who have a more aggressive disease course marked by a rapid accumulation of physical and cognitive deficit. This disease phenotype has been referred to as “aggressive” MS; more recently, “highly active” MS is commonly identified based on relapse frequency, relapse severity, relapse recovery, and key lesions on brain scans.[5] However, this term has been used relatively recent among the MS community as the understanding of MS evolves, and there is no consensus on the definition of this MS phenotype.

Current Management

There is no cure for MS. Treatment typically focuses on alleviating CNS inflammation, speeding recovery from attacks, reducing the recurrence of relapses, slowing the progression of the disease (especially disability), and managing MS symptoms. Patients with RRMS are considered for treatment with disease-modifying treatments (DMTs) that are an essential part of the MS treatment pathway. These drugs target the immune response and have been shown to reduce relapse rates, the formation of new or active MRI brain lesions, and slow the disease progression in some patients; however, they do not reverse damage that has already occurred.[9]

In Canada, the DMTs approved for use as initial induction treatments are 5 injectable drugs (glatiramer acetate, 3 formulations of interferon beta-1a, and interferon beta-1b) and 2 oral drugs (teriflunomide and dimethyl fumarate). Two monoclonal antibodies (ocrelizumab and ofatumumab) have recently been approved and reimbursed for use in patients with RRMS.

Although several DMTs are available for patients with RRMS, the optimal sequencing of DMTs throughout the treatment course is uncertain, which adds to the complexity of the treatment landscape and represents a challenge when recommending therapeutic options for individual patients. The choice of treatment needs to be individualized according to disease activity, severity, and comorbidities, and factors such as efficacy, safety and tolerability, and route of administration (oral versus injectable). Availability may also influence treatment selection.

There are 2 treatment approaches for patients who are newly diagnosed with RRMS. The first is an “escalation” approach, which involves initiating (first-line) therapy with a DMT that has relatively fewer serious adverse effects but with moderate efficacy and a modest likelihood of controlling the patient’s disease activity and then escalating to more effective or potent therapies based on continued disease activity and inadequate symptom control. The second approach is the “early high-efficacy treatment” or “early intensive treatment” approach that involves starting therapy with a high-efficacy drug in the first line. This has a greater likelihood of controlling disease activity and symptoms but also has a higher potential for serious adverse events (SAEs), although the actual frequency of these SAEs remains very low. Historically, the escalation approach has been used, with high-efficacy DMTs reserved for patients with poor response to a traditional first-line drug. This approach has been used based on the line of therapy specified in the approved indications, with drugs that have poorer benefit to risk profiles reserved as later-line therapies as well as evidence that many newer, higher-efficacy drugs may have worse cost-effectiveness compared with low-efficacy to moderate-efficacy drugs. However, there has been a paradigm shift in the treatment of MS, and the early highly

effective treatment approach is increasingly preferred. Several observational studies from large MS registries around the world have shown that an early high-efficacy treatment strategy is superior to an escalation treatment approach at preventing disability progression over time.[10-14] Increasingly, there are calls for early and unrestricted access to high-efficacy DMTs for RRMS, especially for those patients with high disease activity.[15-18] The CMSWG now considers high-efficacy DMTs as starting treatment options for patients with high disease activity, aggressive disease presentation, or rapidly evolving symptoms at onset because these patients are at significant risk of disability worsening early in the disease course.[5]

In clinical practice, an increasing number of neurologists prefer the early high-efficacy treatment approach for appropriate patients to the traditional escalation treatment approach. The clinical experts consulted by Canada's Drug Agency (CDA-AMC) for this review noted that the traditional strategy of initiating lower-efficacy treatments first, with the possibility of switching to another DMT if necessary, is still typically used for many patients due to restrictions in the reimbursement criteria that make some high-efficacy DMTs available only in second or later lines of treatment. The clinical experts highlighted that earlier use of high-efficacy DMTs after onset in patients with RRMS — particularly those with high disease activity or rapidly evolving MS — could prevent irreversible damage to the nervous system. This damage may occur in the current traditional sequential escalation approach that requires trial, failure, or intolerance to other options. Six DMTs available in Canada are considered high-efficacy treatments by the CMSWG: fingolimod, cladribine, natalizumab, alemtuzumab, ofatumumab, and ocrelizumab.[5] Only 2 — ofatumumab and ocrelizumab — which are both anti-CD20 B cell–depleting drugs, are currently listed by some of the provincial drug plans as first-line treatment for RRMS.

Unmet Need

RRMS is a seriously debilitating disease that is chronic in nature. Clinical presentation and symptom type and severity are also highly variable from patient to patient. Given the mounting evidence supporting the use of high-efficacy drugs for most patients with RRMS, there is a shift in the treatment paradigm from the traditional escalation treatment approach to the early high-efficacy treatment approach. Currently, there are 2 high-efficacy DMTs reimbursed: ofatumumab (subcutaneous injection) and ocrelizumab (IV infusion). Of note, ofatumumab is not reimbursed across all public drug plans. Both DMTs have the same mechanism of action (B cell–directed therapies). Given the heterogeneity of the patient population with RRMS, there remains an unmet need for high-efficacy DMTs with different mechanisms of action, tolerability profile, and alternative modes of administration, including high-efficacy oral therapies. The clinical experts consulted for this review noted there is an important unmet need for a high-efficacy DMT with fast action for use in patients with high disease activity (e.g., with multiple gadolinium-enhancing lesions or multiple relapses within a year) in need of rapid stabilization. There is also an important unmet need for an orally administered high-efficacy DMT.

Currently, access to some high-efficacy DMTs is restricted to later stages of the disease due to restrictions in reimbursement criteria in which these drugs may be accessed after inadequate response or lack of tolerability to lower-efficacy drugs. Although not every patient should be treated with high-efficacy DMTs at the initial stages of the disease, early and unrestricted access to high-efficacy DMTs with a positive benefit-

risk profile would provide clinicians and patients with a better choice for an appropriate treatment based on patient profile and treatment needs and can improve patient outcomes. Starting appropriate patients on high-efficacy drugs may also facilitate efficient resource allocation if patients are not required to cycle through less effective treatments first to gain access to high-efficacy DMTs.

Review Scope

In 2022, the public drug programs requested a Health Technology Assessment (HTA) to inform their formulary management of first-line drugs for RRMS and whether these drugs should be used as first-line treatments in adults with highly active RRMS given the changes in clinical practice in how MS is treated. The population of patients with highly active RRMS was selected because these patients are considered at high risk of poor outcomes and may particularly benefit from early access to high-efficacy DMTs. Public drug programs identified alemtuzumab, natalizumab, cladribine, fingolimod, and rituximab as drugs of interest. The HTA aimed to assess the clinical efficacy and safety of alemtuzumab, natalizumab, cladribine, fingolimod, and rituximab as first-line treatments in patients with highly active RRMS compared with drugs currently used as first-line treatments in adult patients with highly active RRMS (lower-efficacy drugs: glatiramer acetate, interferon beta-1a and interferon beta-1b, teriflunomide, dimethyl fumarate; highly active DMTs: ocrelizumab and ofatumumab).

The HTA was published in May 2024 and included a systematic review of published randomized controlled trials (RCTs) and prospective comparative cohort studies comparing high-efficacy treatments with current first-line treatments or placebo.[19] The systematic review identified 7 publications reporting results from post hoc subgroup analyses of 5 RCTs and 1 prospective cohort study. The evidence suggested that natalizumab, cladribine, alemtuzumab, and fingolimod may be effective for first-line treatment of adults with highly active RRMS. However, the evidence was based primarily on post hoc subgroup analyses of clinical trials. This is partly because, at the time of most of the original trials, a priori examination of individuals with highly active disease was not a consideration as the science had not evolved sufficiently to identify this group of patients as a relevant subgroup that should be captured for specific or differential examination.

HTA reviews are not accompanied by reimbursement recommendations and proposed reimbursement criteria for public drug plan implementation; therefore, in 2024 the public drug plans requested another review of the evidence comparing high-efficacy drugs with currently used first-line treatment options for highly active RRMS and reimbursement recommendations from the new Formulary Management Expert Committee (FMEC) at CDA-AMC. For this review, the drug plans identified natalizumab and cladribine as the drugs of interest. These 2 drugs were thought to meet a particular unmet need for first-line therapy in select patients that is not met by the 2 high-efficacy drugs currently reimbursed in first line (i.e., ofatumumab and ocrelizumab). Considering the limited evidence identified regarding comparative efficacy and safety of DMTs in the population of patients with highly active RRMS, the review protocol was later amended to expand the review of the clinical evidence to the broader RRMS population. “Highly active RRMS” is a recent term with no established, universally accepted definition, which partly explains the lack of clinical trials to date specifically recruiting these patients. However, some studies have conducted post hoc analyses of this subgroup using varying definitions. The decision to revise the review also considered input provided by

external partners regarding the review scope, which highlighted the challenges in identifying and relying on clinical trial evidence on highly active RRMS.

Drugs

Natalizumab

Natalizumab (brand name: Tysabri) is a recombinant humanized IgG4κ monoclonal antibody selective for alpha-4 integrin on the surface of lymphocytes, which is essential for the process by which lymphocytes gain access to the brain. Natalizumab blocks alpha-4 integrin, preventing lymphocytes from entering the CNS and attacking myelin.[20]

Natalizumab is the first in a class of drugs called *selective adhesion molecule inhibitors* and was the first high-efficacy monoclonal antibody approved as monotherapy for MS. It was initially approved by the US FDA in November 2004 but was withdrawn by the manufacturer in February 2005 after 3 participants in the drug's clinical trials developed progressive multifocal leukoencephalopathy (PML), a rare and serious viral infection of the brain; 2 of the participants died. Following a reassessment of the participants in the previous clinical trials, the FDA allowed a clinical trial of natalizumab to proceed in February 2006. No additional cases of PML were reported, and the FDA concluded that, based on the available information, the clinical benefits of natalizumab outweighed the potential risks, and marketing of the drug for severe RRMS resumed.[21,22]

Natalizumab received a Notice of Compliance from Health Canada in September 2006. Natalizumab is indicated as monotherapy for the treatment of people with RRMS to reduce the frequency of clinical exacerbations and to decrease the number and volume of active brain lesions identified on MRI scans. Natalizumab is generally recommended in patients with MS who have had an inadequate response to, or are unable to tolerate, other therapies for MS.[23] Natalizumab is administered by IV infusion at a recommended dosage of 300 mg every 4 weeks.

Natalizumab was initially reviewed by CADTH in April 2007. The Canadian Expert Drug Advisory Committee (CEDAC) recommended that natalizumab not be listed.[24] In February 2009, a resubmission was reviewed based on a new price and new pharmacoeconomic evaluation, and CEDAC recommended that natalizumab be listed as monotherapy for patients with a diagnosis of MS established according to current clinical criteria and MRI evidence. Patients must also have met all of the following criteria: failure to respond to full and adequate courses of treatment with at least 2 DMTs or have contraindications to or be intolerant of these therapies, significant increase in T2 lesion load compared to a previous MRI or at least 1 gadolinium-enhancing lesion, and 2 or more disabling relapses in the previous year.[25]

The data protection for natalizumab ended on September 28, 2014.[26] No biosimilars have yet been approved in Canada (one is under review). However, biosimilar availability has been reported in the US.[27] Biosimilars are also available in Europe and the UK.[28]

Cladribine

Cladribine (brand name: Mavenclad) is a synthetic chlorinated deoxyadenosine analogue that is biologically active in selected cell types and provides targeted and sustained reduction of circulating T and B

lymphocytes implicated in the pathogenesis of MS. By interfering with a target cell's ability to process DNA, the therapy leads to the depletion of disease-causing lymphocytes and results in reduced inflammation.

Cladribine received a Notice of Compliance from Health Canada in November 2017. Cladribine is indicated as monotherapy for the treatment of adult patients with RRMS to reduce the frequency of clinical exacerbations and delay the progression of disability. It is generally recommended for patients with RRMS who have had an inadequate response to, or are unable to tolerate, 1 or more therapies for RRMS. Cladribine is available as an orally administered tablet, and the Health Canada–approved dosage is 3.5 mg/kg body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year.[29]

Cladribine was reviewed by CADTH in October 2018.[30] The Canadian Drug Expert Committee (CDEC) recommended that cladribine be reimbursed as monotherapy for the treatment of adult patients with RRMS to reduce the frequency of clinical exacerbations and delay the progression of disability if the following conditions were met: for use in patients who have had an inadequate response to, or are unable to tolerate, 1 previous therapy for RRMS, and who have had at least 1 relapse within the previous 12 months; the patient is under the care of a specialist who has experience in the diagnosis and management of RRMS; and there is a price reduction. CDEC aligned their recommendations with the Health Canada indication for cladribine, which is that it is generally recommended for patients with RRMS who have had an inadequate response to, or are unable to tolerate, 1 or more therapies for RRMS; however, most patients enrolled in the CLARITY trial were had not received prior treatment. Health Canada expressed concern about the higher proportions of patients treated with cladribine in the CLARITY trial who experienced certain notable adverse events (AEs) compared with placebo, such as lymphopenia, herpes zoster infection, and neoplasms. As a result, Health Canada's benefit-risk evaluation for cladribine was that it should generally not be used as a first-line drug in the treatment of RRMS.

The data protection end date is not available for cladribine. Two generics are under review by Health Canada. However, details for these submissions (e.g., oral versus parenteral) are not available. Two generics are currently marketed for parenteral cladribine.

Input From External Partners

External partners had the opportunity to provide input on the proposed review scope. The following section is a summary of their input. The full input submitted is posted on the CDA-AMC website. Input was provided on the original review scope, which included patients with highly active RRMS, before the scope was expanded to the broader population of patients with RRMS.

Patient Group

MS Canada provided input on this review. It was noted in the input that current drug policy in Canada rarely allows people living with MS to initiate treatment with a high-efficacy therapy because of strict reimbursement criteria. Current reimbursement practices follow an escalation approach, which is based on limited evidence. Despite the significant advances in our understanding of the pathophysiology of MS and the development of innovative and highly effective therapies, treatment approaches have not evolved to reflect these advancements and public drug plans continue to use the escalation approach as the foundational framework

in reimbursements. MS Canada emphasized the increasing shift to treat people with highly active MS with high-efficacy DMTs as early as possible to avoid neurological damage and irreversible disability caused by suboptimal management of disease activity. They cited US and Canadian clinical practice guidelines that are clear in their recommendations for initiating treatment with a high-efficacy DMT in individuals with high disease activity at the time of diagnosis. MS Canada's input also highlighted the need for high-efficacy DMTs with varied mechanisms of action to address the heterogeneity of the disease response to DMTs and to place the patient at the centre of their disease management.

MS Canada noted the lack of head-to-head comparison studies is a long-standing challenge in the pharmacoeconomic review of MS DMTs for public payer decision-making. There are no MS DMTs formally indicated as first-line treatments for individuals with "highly active relapsing MS"; as such, MS Canada did not believe that it was possible to adequately answer the question of whether these high-efficacy DMTs are effective for treatment of people with highly active RRMS and that the review scope did not reflect the perspective of a patient group and meaningfully address the current needs of this subpopulation of Canadians living with highly active RRMS.

Clinician Group

The Canadian Network of Multiple Sclerosis Clinics (CNMSC), a national network of academic and community-based clinics established for the advancement of patient services, education, and research in MS, provided input on the scope of this review. CNMSC had previously provided extensive input on the HTA scope, list of included studies, and draft report for the HTA from the initiation of the review in 2022 to the publication of the report in 2024. Because the previous input on the HTA remained relevant to the current review, it was resubmitted to CDA-AMC in addition to new input on the current review scope.

CNMSC noted that having options readily available for select patients, including those with aggressive disease, is critical in their efforts as practitioners to provide the best care for their patients and avoid serious disability. CNMSC appreciated the recognition of the change in the approach to optimal management of MS and 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 patients, particularly those with highly active disease. CNMSC emphasized 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 outcomes in persons living with MS as well as direct (i.e., health system) and indirect (i.e., productivity, social assistance) costs. They further highlighted that 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 the globally accepted standards for disease management in MS.

In its input regarding the HTA, CNMSC expressed concern about the literature search terms used by CADTH and the expectation of identifying clinical trials focused solely on the patient population with "aggressive or highly active" MS. They highlighted that using the search terms "aggressive or highly active MS" is unlikely to reveal the full evidence base to address the key question for the review. 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 of patients. Historically, there were many patients with highly active MS enrolled in clinical

trials because of the very limited treatment options available at the time of pivotal trials and because designation of “highly active” MS was not part of the diagnostic paradigm at the time. As a result, clinical trial results for many MS drugs include, and therefore reflect, the impact of these drugs on this patient population. For instance, CNMSC indicated that the original phase III RCTs for natalizumab (and the other DMTs) should have been within scope for the HTA because they were all first-line studies and included this patient population. They also disagreed with the exclusion of trials without an active comparator, noting that evidence from placebo-controlled trials should not be excluded given the context of the history of MS drug development and understanding that, at the time of the trials, placebo-controlled comparisons were valuable in addressing the question of the drug’s efficacy and safety. Furthermore, excluding these studies would disadvantage some drugs, such as natalizumab, that were studied at a time when there were few other therapies available.

In the input for the current review, CNMSC reiterated the issues regarding limited clinical trial data for natalizumab and cladribine compared with other DMTs in patients with highly active RRMS and the need for including real-world evidence to inform the review on the efficacy and safety of these drugs in this population. CNMSC believed that the relevant policy question should be whether there is sufficient evidence of effectiveness for natalizumab and for cladribine in the first-line setting (rather than a comparison with other DMTs used in first line, including low-efficacy DMTs stated in the review scope). They also suggested considering the harm of not starting high-efficacy treatments in patients with highly active disease because of the clinical or disability and economic implications of delayed therapy. CNMSC also raised the issue of equitable access, noting that some provinces already fund these drugs on a case-by-case basis, including Quebec which funds natalizumab for patients with highly active disease.

Industry

Biogen, the manufacturer of natalizumab, and EMD Serono, the manufacturer of cladribine, provided input on the project scope.

Biogen agreed that the project scope would be useful in decision-making but noted the absence of a prespecified definition of highly active MS from the project scope. They requested that the new review also include real-world studies and noncomparative, prospective, long-term studies to inform on the safety and durability of efficacy of natalizumab. The input also provided a list of key natalizumab trials and observational studies of natalizumab that the manufacturer suggested be included in the review.

EMD Serono regretted that findings from the HTA were not translated into listing criteria for public drug plan implementation. They urged FMEC to proceed to the recommendation phase in the absence of new significant clinical evidence since the publication of the HTA in May 2024.

Policy Question

Should natalizumab and cladribine be reimbursed in the first line for treatment of people with RRMS?

Clinical Review

Objectives

The objective of this review is to:

- identify the highest quality and most relevant evidence regarding the efficacy and safety of natalizumab and cladribine compared with other DMTs used in first line for treating people with RRMS
- summarize feedback from patients, clinicians, and manufacturer perspectives on the needs for first-line therapies for RRMS
- compare costs for natalizumab and cladribine with other DMTs currently reimbursed for first-line treatment of people with RRMS.

Methods

The streamlined drug review was chosen for the need to provide a timely appraisal of the evidence regarding the comparative efficacy and safety of natalizumab and of cladribine with other currently reimbursed first-line DMTs. Following the initial scoping phase, the review's scope was amended to include all patients with RRMS regardless of disease severity or rate of progression. This broader scope allowed for more clinical trial data to be considered as the evidence base for the review. However, there are few direct comparison trials, which would provide the most rigorous research evidence on the relative efficacy and safety of different treatments. Network meta-analyses or multiple treatment meta-analyses allow a robust alternative method for comparison of multiple treatments simultaneously when head-to-head trials are lacking. Network meta-analyses are particularly valuable for informing policy decisions when key treatment comparisons are unavailable. This streamlined drug review will focus on summarizing the best available evidence, leveraging the most comprehensive and rigorously conducted systematic reviews and network meta-analyses that address the policy question.

Search Methods

An information specialist performed the literature search for clinical studies, using a peer-reviewed search strategy according to the CDA-AMC PRESS Peer Review of Electronic Search Strategies checklist. Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multifile search. Search concepts were developed based on the elements of the PICOS (population, intervention, comparison, outcome, and study) framework and research questions. The main search concepts were RRMS and natalizumab or cladribine. CDA-AMC developed search filters that were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or indirect treatment comparisons. Conference abstracts were excluded from the search results. Retrieval was not limited by publication date or by language. Refer to Appendix 1 for the detailed search strategies. The initial search was completed on September 20, 2024. Regular alerts continued to update the search until December 2, 2024.

Selection Process

One reviewer screened the titles and abstracts of the screened citations for relevance to the review based on the selection criteria outlined in Table 1. Studies that met the PICOS design criteria were selected for inclusion. In the first level of screening, titles and abstracts were reviewed; potentially relevant articles were retrieved, and their full texts were examined. This included reviewing the primary studies included in the systematic reviews and network meta-analyses to determine primary study overlap.

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart of the study selection is included in Appendix 2. The literature search identified 445 records of which 426 were excluded by screening title and abstract; 19 full-text reports were retrieved. All 19 reports included a network meta-analysis that met the inclusion criteria (i.e., had a relevant population, included a comparison of natalizumab or cladribine with at least 1 comparator of interest, and included an outcome of interest). The characteristics of these studies, including number of studies included in the network meta-analysis, treatment comparisons, and source of funding, were extracted. There was overlap of primary studies across the network meta-analyses. To avoid overlap and redundancy in primary studies, the most recent and comprehensive systematic review with network meta-analysis that included comparison of natalizumab or cladribine with all the comparator drugs of interest was included (i.e., systematic reviews and network meta-analyses in which all relevant composing primary studies were captured in another more recent analysis were sequentially excluded). Excluded studies are listed in Appendix 3.

One systematic review with a network meta-analysis that evaluated therapies for the treatment of people with RRMS was included, Immunomodulators and Immunosuppressants for Relapsing-Remitting Multiple Sclerosis: A Network Meta-Analysis.[31] This systematic review with network meta-analysis is an update of a Cochrane review published in 2015.[32] This network meta-analysis is the most comprehensive and up-to-date synthesis of direct and indirect evidence from clinical trials published by an academic group regarding the comparative efficacy of different therapies for RRMS, and it forms the evidence base for this streamlined drug review.

Table 1: Study Selection Criteria

Criteria	Description
Population	Patients with RRMS who are DMT-naive
Interventions	• Natalizumab (Tysabri), 300 mg IV infusion every 4 weeks • Cladribine (Mavenclad), 3.5 mg/kg orally over the course of 2 years, administered as 1 treatment course of 1.75 mg/kg per year
Comparators[a]	• Glatiramer acetate • Interferon beta-1a • Interferon beta-1b • Teriflunomide • Dimethyl fumarate • Ocrelizumab • Ofatumumab

Criteria	Description
Outcomes	**Efficacy:** • relapse • disability progression • function • imaging outcomes (e.g., MRI brain lesions, MRI brain volume, spinal cord imaging) • cognitive outcomes • symptoms (e.g., fatigue, cognition, mobility, visual disturbance) • HRQoL • instrumental activities of daily living (e.g., absenteeism, presentism, employment status) **Harms:** • adverse events • serious adverse events • withdrawal due to adverse events • mortality Notable adverse events: injection-related reactions, opportunistic infections, serious infections, progressive multifocal leukoencephalopathy, lymphopenia, neutropenia, malignancies
Study design	Systematic reviews of RCTs with network meta-analysis
Search dates	Up to September 20, 2024 (no date limits)

DMT = disease-modifying therapy; HRQoL = health-related quality of life; MS = multiple sclerosis; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis.

[a]DMTs that are currently reimbursed in Canada for RRMS in first line.

Summary of Evidence

Methods of the Included Network Meta-Analysis

The Cochrane systematic review and network meta-analysis by Gonzalez-Lorenzo et al. (2024)[31] compared the efficacy and safety of different therapies for RRMS. The authors of the network meta-analysis considered all immunomodulators and immunosuppressants that, up to September 2021, have been studied in people with RRMS in RCTs with at least 12 months' follow-up. Characteristics of the Cochrane review are summarized in Table 2.

Participants

The Cochrane review included adult participants aged 18 years or older with a diagnosis of RRMS, according to Poser or McDonald diagnostic criteria,[33-36] regardless of sex, degree of disability, and disease duration.

Interventions

All immunomodulators or immunosuppressants (even if they were not licensed in any country) were included. Combination treatments, trials in which a drug regimen was compared with a different regimen of the same drug without another active drug or placebo as a control arm, nonpharmacological treatments, and over-the-counter drugs were not considered. The review included RCTs that evaluated 1 or more of the following pharmacological interventions as monotherapy, compared with placebo, or compared to another active drug: interferon beta-1b, interferon beta-1a, glatiramer acetate, natalizumab, mitoxantrone, fingolimod,

teriflunomide, dimethyl fumarate, alemtuzumab, pegylated interferon beta-1a, daclizumab, laquinimod, azathioprine, immunoglobulins, cladribine, cyclophosphamide, diroximel fumarate, fludarabine, interferon beta-1a and beta-1b, leflunomide, methotrexate, minocycline, mycophenolate mofetil, ofatumumab, ozanimod, ponesimod, rituximab, siponimod, and steroids.

Outcome Measures

Gonzalez-Lorenzo et al. estimated the relative effects of the competing interventions according to the following primary efficacy and safety outcomes:

- Relapses (over 12, 24, or 36 months), defined as newly developed or recently worsened symptoms of neurological dysfunction lasting for at least 24 hours, occurring in the absence of fever or other acute diseases, and separated in time from any previous episode by more than 30 days.[33,35] Relapse can resolve either partially or completely.
- Disability worsening (over 24 or 36 months), defined as an increase of at least a 1 point on the Expanded Disability Status Scale (EDSS) or of 0.5 points if the baseline EDSS was greater than or equal to 5.5, confirmed during 2 subsequent neurological examinations separated by at least a 6-month interval without relapses. Disability worsening confirmed after only 3 months of follow-up is considered a surrogate marker for unremitting disability. EDSS is a common measure of MS disability and is used in MS clinical trials to assess disability worsening (0 = normal, 3 = mild disability, 6 = care requirement, 7 = wheelchair use, and 10 = death from MS).
- Discontinuation due to AEs.
- SAEs, measured as the number of participants with any (1 or more) SAEs and defined according to the authors of the included study.

Secondary outcomes included cognitive decline, quality of life impairment, new or enlarging T2-weighted MRI lesions, new gadolinium-enhancing positive T1-weighted MRI lesions, and MS-related mortality.

Assessment of Risk of Bias

The risk of bias in each included study was assessed using the Cochrane Collaboration's tool for assessing the risk of bias. The bias domains include random sequence generation, allocation concealment, blinding of participants and providers, blinding of outcome assessor(s), incomplete outcome data, and selective outcome reporting, as well as the role of the sponsor. Each study was judged on each criterion and classified as being at low, high, or unclear risk of bias. Sensitivity analyses were performed including only the trials with low risk of selection and attrition bias.

Data Synthesis

Relative treatment effects were reported as risk ratios (RRs) and 95% CIs for dichotomous outcomes. Peto odds ratios (ORs) with 95% CIs were reported if the number of observed events was less than 5% of the sample per group. Mean differences or standardized mean differences were reported for continuous outcomes. The results of the network meta-analysis were presented as summary relative effect sizes (RR, mean difference, or standardized mean difference) for each possible pair of treatments.

A network meta-analysis was performed using a random-effects model within a frequentist setting assuming equal heterogeneity across all comparisons and accounted for correlations in multiarm studies. Also assessed was statistical heterogeneity and statistical inconsistency for the network meta-analysis models.

Assessment of the Certainty of Evidence

The authors presented the main results of the review in a Summary of Findings (SoF) table; and assessed the certainty of the network meta-analysis estimates for the primary outcome measures using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Because the results of the Cochrane review were intended to serve as the evidence base for guidance on the use of DMTs in people with RRMS, the certainty of the evidence was assessed using a fully contextualized approach that incorporated the value of individual outcomes in the overall interpretation of the results. This involved predefining quantitative thresholds to determine the magnitude of each health effect measured by means of each outcome. The magnitudes of health effects were defined according to the GRADE wording as trivial, small, moderate, and large. Assessment of imprecision followed the GRADE guidance using a fully contextualized approach. The certainty of evidence for each outcome was graded considering study limitations, indirectness, inconsistency, imprecision of effect estimates, and risk of reporting bias by assigning 4 levels of certainty of evidence: high, moderate, low, and very low.

Table 2: Characteristics of the Cochrane Review of Treatments for RRMS

Characteristic	Description
Number of studies	50
Number of patients	36,541
Number of placebo-controlled trials	25
Number of head-to-head trials with other treatments	25
Median treatment duration	24 months (4 studies reported 36-month follow-up)
Patient population	Adults aged 18 years or older with a diagnosis of RRMS
Treatments compared	Interferon beta-1b, interferon beta-1a, glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, pegylated interferon beta-1a, daclizumab, laquinimod, azathioprine, immunoglobulins, cladribine, cyclophosphamide, diroximel fumarate, fludarabine, interferon beta-1a and beta-1b, leflunomide, methotrexate, minocycline, mycophenolate mofetil, ofatumumab, ocrelizumab, ozanimod, ponesimod, rituximab, siponimod, and steroids
Outcome measures	**Primary outcomes:** • relapse (proportion of participants who experienced new relapses over 12, 24, or 36 months after randomization or at the end of the study) • disability worsening (proportion of participants who experienced disability worsening over 24 or 36 months after randomization or at the end of the study) • discontinuation due to AEs • SAEs

Characteristic	Description
	Secondary outcomes: • cognitive decline (variation in the score of SDMT or PASAT) • quality of life impairment (variation in the score of any scale reporting quality of life impairment) • new or enlarging T2-weighted MRI lesions (number or participants with new or enlarging T2-weighted lesions at 12, 24, 36 months after randomization) • new gadolinium-enhancing positive T1-weighted MRI lesions (number of participants with new gadolinium-enhancing T1-weighted MRI lesions at 12, 24, and 36 months after randomization) • mortality (overall number of MS-related deaths)
Previous treatment	Of the 50 studies: • 1 included only those previously treated with DMTs • 5 included only those previously untreated with DMTs • 17 did not report data about previous treatments with DMTs • 27 included a mixed population of patients with and without previous treatment with DMTs but did not report separate outcome data

AE = adverse event; DMT = disease-modifying treatment; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; PASAT = Paced Auditory Serial Addition Test; RRMS = relapsing-remitting multiple sclerosis; SAE = serious adverse event; SDMT = Symbol Digit Modalities Test.

Description of the Studies Included in the Network Meta-Analysis

The Cochrane review included 50 studies involving 36,541 participants (68.6% female; 31.4% male) and published between 1987 and 2021. Twenty-five studies were placebo-controlled and 25 were head-to-head studies. Of the 50 included studies, 7 studies included a mixed sample of participants with not only relapsing but also other forms of MS; only those with more than 80% of the sampled population affected by relapsing forms of MS were included in the analyses.

Of the 50 included studies, 1 included only people with MS previously treated with DMTs, 5 included only people with MS previously untreated with DMTs, 17 did not report data about previous treatments with DMTs, and 27 included a mixed population of patients with and without previous treatment with DMTs but did not report separate outcome data for the 2 subgroups.

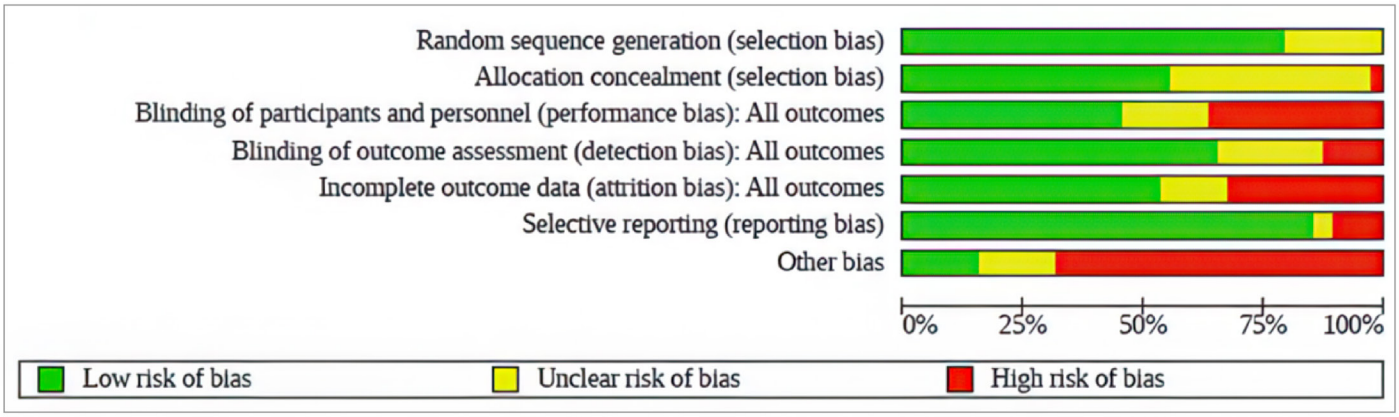
Median follow-up was 24 months, including follow-up at 12 months (n = 11), 18 months (n = 1), 24 months (n = 32), 25 months (n = 1), 30 months (n = 2), and 36 months (n = 4).

Risk of Bias in Included Studies

The risk of bias assessments with review authors' judgment for each risk of bias item (presented as percentages across all included studies) are summarized in Figure 1.Regarding the 6 domains for which risk of bias were assessed, 40 studies (80%) reported adequate detail to assess sequence generation and were at low risk of bias for sequence generation and 38 studies (76%) were at low risk for allocation concealment (the cladribine CLARITY trial was judged as unclear bias for this domain). For blinding of participants and personnel (performance bias), 24 studies (48%) were at low risk of bias, 9 (18%) did not provide sufficient information and were at unclear risk of bias, and 17 (34%) were unblinded and were at high risk of bias. For blinding of outcome assessors (detection bias), 33 studies (66%) were at low risk of bias, 11 (22%) did not

provide sufficient information and were at unclear risk, and 6 (12%) were at high risk of bias. For 27 studies (54%), incomplete outcome data appeared to have been adequately addressed, and any missing outcome data were reasonably well-balanced across intervention groups, with similar reasons for missing data across the groups with low risk of bias. Seven studies (14%) did not provide sufficient information with unclear risk of bias and 16 (32%) of included studies were at high risk of bias due to incomplete outcome data. For selective reporting, 43 studies (86%) reported all prespecified primary outcomes and were at low risk of bias, 2 studies (4%) were at unclear risk of bias (including the cladribine CLARITY trial), and 5 (10%) were judged to be at high risk of bias for selective outcome reporting due to lack of reporting of all prespecified outcomes. Thirty-four studies (68%), which includes the AFFIRM trial for natalizumab and CLARITY trial for cladribine, were judged to be at high risk of other bias, including role of the sponsor in authorship of the study or data management; 8 (16%) were at unclear risk of bias and 8 (16%) were at low risk of bias for this domain.

Figure 1: Risk of Bias Assessment Across All Included Studies in the Network Meta-Analysis



Source: Reprinted with permission (CC BY-NC) from Gonzalez-Lorenzo et al. (2024), Figure 2.[31]

Results of the Network Meta-Analysis

Gonzalez-Lorenzo et al. reported treatment estimates from pairwise meta-analyses (direct comparisons, mostly with placebo) and network meta-analysis estimates combining direct and indirect comparisons of treatment versus placebo and versus each of the other included treatments. The findings of the network meta-analyses are summarized subsequently.

Primary Outcomes

Relapses

Relapses over 12 months: Data were reported in 18 studies involving 9,310 participants with RRMS (25.49% of the participants in the review) and assessing 13 treatments. Nine treatments assessed in 18 studies were compared with placebo, of which 7 treatments were evaluated in head-to-head comparisons in 7 studies.

Using placebo as a common comparator, treatment with natalizumab resulted in a large reduction in the number of people experiencing relapses (RR = 0.52; 95% CI, 0.43 to 0.63; high-certainty evidence).

The network estimates of relapses are summarized in Table 3 for selected treatments of interest:

- Treatment with natalizumab resulted in a greater reduction in the number of people experiencing relapses over 12 months compared with interferon beta-1a and beta-1b and interferon beta-1a. There was no difference with respect to other treatments.
- There were insufficient data available to evaluate cladribine in comparison with other treatments for this outcome.

Relapses over 24 months: Data were reported in 28 studies involving 19,869 participants with RRMS (54.4% of those included in the review) and assessing 15 treatments. Twelve treatments, assessed in 21 studies, were compared with placebo; 10 treatments were evaluated in head-to-head comparisons in 11 studies and 2 studies including 2,751 participants had both placebo and active treatment arms.

Using placebo as a common comparator, treatment with cladribine (RR = 0.53; 95% CI, 0.44 to 0.64; high-certainty evidence) or natalizumab (RR = 0.56; 95% CI, 0.48 to 0.65; high-certainty evidence) resulted in a large decrease in the number of people experiencing relapses.

The network estimates of relapses are summarized in Table 3 for selected treatments of interest:

- Treatment with natalizumab resulted in a greater reduction in the number of people experiencing relapses over 24 months compared with glatiramer acetate, interferon beta-1a and beta-1b, interferon beta-1a, interferon beta-1b, and teriflunomide. No data were available for comparison with ocrelizumab and ofatumumab for this outcome.
- Treatment with cladribine resulted in a greater reduction in the number of people experiencing relapses over 24 months compared with glatiramer acetate, interferon beta-1a and beta-1b, interferon beta-1a, interferon beta-1b, and teriflunomide. No data were available for comparison with ocrelizumab and ofatumumab for this outcome.

Relapses over 36 months: Data were reported in 5 studies involving 3,087 participants with RRMS (8.4% of the participants in the review) and assessing 5 treatments. None of these studies compared natalizumab or cladribine with other treatments for this outcome.

Table 3: Relapses Over 12 and 24 Months

	12 months, RR (95% CI)		24 months, RR (95% CI)	
Comparator[a]	Natalizumab	Cladribine	Natalizumab	Cladribine
Glatiramer acetate	0.80 (0.63 to 1.02)	NA	0.67 (0.55 to 0.81)	0.63 (0.51 to 0.78)
Interferon beta-1a and beta-1b	0.36 (0.19 to 0.68)	NA	0.46 (0.25 to 0.86)	0.44 (0.23 to 0.82)
Interferon beta-1a	0.68 (0.55 to 0.85)	NA	0.66 (0.56 to 0.79)	0.63 (0.51 to 0.77)
Interferon beta-1b	NA	NA	0.66 (0.55 to 0.80)	0.62 (0.50 to 0.77)
Interferon beta-1b (Betaferon)	0.63 (0.38 to 1.07)	NA	NA	NA
Teriflunomide	0.79 (0.61 to 1.01)	NA	0.68 (0.55 to 0.84)	0.64 (0.51 to 0.81)
Dimethyl fumarate	NA	NA	0.90 (0.74 to 1.10)	0.85 (0.68 to 1.06)

Comparator[a]	12 months, RR (95% CI)		24 months, RR (95% CI)	
	Natalizumab	Cladribine	Natalizumab	Cladribine
Ocrelizumab	NA	NA	NA	NA
Ofatumumab	NA	NA	NA	NA

CI = confidence interval; NA = not available; RR = risk ratio.

[a]Only data for the treatments of interest to this review were extracted from the network meta-analysis netleague tables.

Source: Adapted with permission (CC BY-NC) from Gonzalez-Lorenzo et al. (2024), Tables 2 and 3.[31]

Disability Worsening

Disability worsening over 24 months: Data were reported in 31 studies including 24,303 participants with RRMS (66.5% of those included in the review) and assessing 18 treatments. Eleven treatments, assessed in 20 studies, were compared with placebo, 13 treatments were evaluated in head-to-head comparisons in 15 studies, and 2 studies (2,751 participants) had both placebo and active treatment arms.

Using placebo as a common comparator, treatment with natalizumab probably results in a moderate reduction in the number of people experiencing disability worsening (RR = 0.59; 95% CI, 0.46 to 0.75; moderate-certainty evidence) and treatment with cladribine may result in a small reduction in the number of people experiencing disability worsening (RR = 0.72; 95% CI, 0.56 to 0.91; low-certainty evidence).

The network estimates of disability worsening are summarized in Table 4 for select treatments of interest:

- Treatment with natalizumab resulted in a greater reduction in the number of people experiencing disability worsening over 24 months compared only with interferon beta-1a. There was no difference between treatment with natalizumab and other select treatment comparators regarding the number of people experiencing disability worsening over 24 months.
- There was no difference between treatment with cladribine and other select treatment comparators regarding the number of people experiencing disability worsening over 24 months.

Disability worsening over 36 months: Data were available from 3 studies involving 2,684 participants with RRMS (7.3% of those included in the review) and assessing 4 treatments. None of these studies compared natalizumab or cladribine with other treatments for this outcome.

Table 4: Disability Worsening Over 24 months

Comparator[a]	Natalizumab, RR (95% CI)	Cladribine, RR (95% CI)
Glatiramer acetate	0.80 (0.59 to 1.09)	1.03 (0.76 to 1.41)
Interferon beta-1a and beta-1b	0.19 (0.02 to 1.96)	4.45 (0.42 to 47.01)
Interferon beta-1a	0.64 (0.46 to 0.90)	1.29 (0.92 to 1.80)
Interferon beta-1b	0.77 (0.56 to 1.07)	1.07 (0.78 to 1.47)
Teriflunomide	0.77 (0.56 to 1.07)	1.07 (0.77 to 1.48)
Dimethyl fumarate	0.91 (0.67 to 1.22)	0.91 (0.68 to 1.23)
Ocrelizumab	0.98 (0.61 to 1.55)	0.85 (0.53 to 1.34)

Comparator[a]	Natalizumab, RR (95% CI)	Cladribine, RR (95% CI)
Ofatumumab	1.09 (0.71 to 1.68)	0.76 (0.49 to 1.16)

CI = confidence interval; RR = risk ratio.

[a]Only data for the treatments of interest to this review were extracted from the network meta-analysis netleague tables.

Source: Adapted with permission (CC BY-NC) from Gonzalez-Lorenzo et al. (2024), Table 5.[31]

Treatment Discontinuation Due to AEs

Data for treatment discontinuation due to AEs were available from 43 studies including 35,410 participants with RRMS (96.9% of those included in the review) and assessing 19 treatments. Thirteen treatments, assessed in 24 studies, were compared with placebo, 16 treatments were evaluated in head-to-head comparisons in 21 studies and 2 studies involving 2,751 participants had both placebo and active treatment arms.

Using placebo as a common comparator, treatment with natalizumab probably results in a trivial increase in the number of people who discontinued due to AEs (OR = 1.57; 95% CI, 0.81 to 3.05) and treatment with cladribine may result in a trivial increase in the number of people who discontinued due to AEs (OR = 1.38; 95% CI, 0.46 to 4.15; low-certainty evidence).

The network estimates of treatment discontinuation due to AEs are summarized in Table 5 for select treatments of interest:

- There was no difference between treatment with natalizumab or cladribine and with other select treatment comparators regarding the number of people discontinuing treatment due to AEs.

Table 5: Treatment Discontinuation Due to AEs

Comparator[a]	Natalizumab, RR (95% CI)	Cladribine, RR (95% CI)
Glatiramer acetate	1.06 (0.50 to 2.27)	1.07 (0.33 to 3.41)
Interferon beta-1a and beta-1b	1.33 (0.11 to 16.69)	2.19 (0.15 to 30.92)
Interferon beta-1a	1.06 (0.49 to 2.30)	1.07 (0.33 to 3.44)
Interferon beta-1b	0.69 (0.26 to 1.88)	1.64 (0.43 to 6.30)
Teriflunomide	1.16 (0.53 to 2.55)	1.32 (0.41 to 4.29)
Dimethyl fumarate	1.16 (0.55 to 2.48)	0.98 (0.31 to 3.12)
Ocrelizumab	0.52 (0.20 to 1.34)	1.69 (0.47 to 6.13)
Ofatumumab	1.27 (0.51 to 3.20)	1.45 (0.40 to 5.18)

AE = adverse event; CI = confidence interval; RR = risk ratio.

[a]Only data for the treatments of interest to this review were extracted from the network meta-analysis netleague tables.

Source: Adapted with permission (CC BY-NC) from Gonzalez-Lorenzo (2024), Table 7.[31]

Serious Adverse Events

Data for SAEs were available from 35 studies including 33,998 participants with RRMS (93% of those included in the review) and assessing 17 treatments. Eleven treatments, assessed in 18 studies, were

compared with placebo, 14 treatments were evaluated in head-to-head comparisons in 21 studies, and 2 studies involving 2,751 participants had both placebo and active treatment arms.

Compared with placebo, treatment with natalizumab may result in a trivial increase in the number of people who experience SAEs (OR = 1.24; 95% CI, 0.73 to 2.09; low-certainty evidence) and treatment with cladribine may result in a trivial increase in the number of people experiencing SAEs, but the evidence is very uncertain (OR = 1.39; 95% CI, 0.80 to 2.40; very low–certainty evidence).

The network estimates of SAEs are summarized in Table 6 for select treatments of interest:

- There was no difference between treatment with natalizumab or cladribine and with other select treatment comparators regarding the number of people experiencing SAEs.

Table 6: Serious Adverse Events

Comparator[a]	Natalizumab, RR (95% CI)	Cladribine, RR (95% CI)
Glatiramer acetate	1.32 (0.72 to 2.43)	0.68 (0.36 to 1.27)
Interferon beta-1a	1.02 (0.55 to 1.90)	0.87 (0.46 to 1.65)
Interferon beta-1b	1.34 (0.65 to 2.78)	0.67 (0.31 to 1.41)
Teriflunomide	0.93 (0.50 to 1.76)	0.83 (0.43 to 1.60)
Dimethyl fumarate	1.19 (0.62 to 2.29)	0.75 (0.38 to 1.46)
Ocrelizumab	0.81 (0.38 to 1.72)	0.72 (0.33 to 1.56)
Ofatumumab	1.22 (0.58 to 2.58)	1.09 (0.51 to 2.35)

CI = confidence interval; RR = risk ratio.

[a]Only data for the treatments of interest to this review were extracted from the network meta-analysis netleague tables.

Source: Adapted with permission (CC BY-NC) from Gonzalez-Lorenzo et al. (2024), Table 8.[31]

Secondary Outcomes

New Gadolinium-Enhancing Positive T1-Weighted MRI Lesions

New gadolinium-enhancing T1 lesions at 12 months: Data were reported in 6 studies involving 5,212 participants with RRMS (14.3% of those included in the review). Two treatments assessed in 2 studies were compared with placebo.

Using placebo as a common comparator, treatment with natalizumab resulted in a large reduction in new gadolinium-enhancing positive T1-weighted MRI lesions (RR = 0.11; 95% CI, 0.07 to 0.17).

New gadolinium-enhancing T1 lesions at 24 months: Data were reported in 11 studies involving 7,935 participants with RRMS (21% of those included in the review) and assessing 11 treatments. Four treatments assessed in 3 studies were compared with placebo, 7 treatments were evaluated in head-to-head comparisons in 9 studies, and 1 study involving 1,417 participants had both placebo and active treatment arms.

Using placebo as a common comparator, natalizumab resulted in a large reduction in new gadolinium-enhancing positive T1-weighted MRI lesions (RR = 0.11; 95% CI, 0.07 to 0.17).

No studies assessed new gadolinium-enhancing positive T1-weighted MRI lesions at 36 months.

The network estimates of new gadolinium-enhancing T1 lesions at 24 months are summarized in Table 7 for select treatments of interest:

- Natalizumab is more effective than glatiramer acetate, interferon beta-1a, and dimethyl fumarate in reducing T1 lesions at 24 months. No comparative data were available for this outcome with ofatumumab.
- There were no data comparing cladribine with other treatments for this outcome.

Table 7: New Gadolinium-Enhancing Positive T1-Weighted MRI Lesions at 24 Months

Comparator[a]	Natalizumab, RR (95% CI)	Cladribine, RR (95% CI)
Glatiramer acetate	0.18 (0.10 to 0.33)	NA
Interferon beta-1a	0.32 (0.16 to 0.62)	NA
Interferon beta-1b	0.68 (0.30 to 1.56)	NA
Teriflunomide	NA	NA
Dimethyl fumarate	0.22 (0.12 to 0.38)	NA
Ocrelizumab	0.86 (0.42 to 1.76)	NA
Ofatumumab	NA	NA

CI = confidence interval; NA = not available; RR = risk ratio.

[a]Only data for the treatments of interest to this review were extracted from the network meta-analysis netleague tables.

Source: Adapted with permission (CC BY-NC) from Gonzalez-Lorenzo et al. (2024), Appendix 7.[31]

New or Enlarging T2-Weighted MRI Lesions

New or enlarging T2-weighted MRI lesions at 12 months: Data were reported in 7 studies involving 5,234 participants with RRMS (14.32% of those included in the review) and assessing 7 treatments. Two treatments, assessed in 2 studies, were compared to placebo, and 6 treatments were evaluated in head-to-head comparisons in 5 studies.

Using placebo as a common comparator, treatment with natalizumab may have resulted in a large increase in new or enlarging T2-weighted MRI lesions (RR = 2.01; 95% CI, 0.43 to 9.51).

The network estimates of new or enlarging T2-weighted MRI lesions at 12 months are summarized in Table 8 for select treatments of interest:

- There was no difference between natalizumab and glatiramer acetate, interferon beta-1a, and interferon beta-1b in reducing new or enlarging T2-weighted MRI lesions. No data were available regarding other select treatments. There were insufficient data comparing cladribine to other treatments for this outcome.

New or enlarging T2-weighted MRI lesions at 24 months: Data were reported in 10 studies involving 6,893 participants with RRMS (19% of those included in the review) and assessing 10 treatments. Two treatments, assessed in 2 studies, were compared with placebo.

Using placebo as a common comparator, treatment with natalizumab resulted in a large reduction in new or enlarging T2-weighted MRI lesions (RR = 0.50; 95% CI, 0.45 to 0.55).

Table 8: New or Enlarging T2-Weighted MRI Lesions at 12 Months

Comparator[a]	Natalizumab, RR (95% CI)	Cladribine, RR (95% CI)
Glatiramer acetate	0.85 (0.72 to 1.01)	NA
Interferon beta-1a	3.98 (0.86 to 18.45)	NA
Interferon beta-1b	0.95 (0.89 to 1.02)	NA
Teriflunomide	NA	NA
Dimethyl fumarate	NA	NA
Ocrelizumab	NA	NA
Ofatumumab	NA	NA

CI = confidence interval; NA = not available; RR = risk ratio.

[a]Only data for the treatments of interest to this review were extracted from the network meta-analysis netleague tables.

Source: Adapted with permission (CC BY-NC) from Gonzalez-Lorenzo et al. (2024), Appendix 8.[31]

Cognitive Decline

Cognitive decline data were available from 6 studies involving 4,243 participants with RRMS (11.6% of those included in the review) and assessing 7 treatments. No studies were compared with placebo, and 6 treatments were evaluated in head-to-head comparisons in 7 studies.

The network estimates of cognitive decline are summarized in Table 9 for select treatments of interest:

- Treatment with natalizumab resulted in slower cognitive decline compared with treatment with glatiramer acetate or interferon beta-1a. There were no data comparing natalizumab with other selected treatments.
- There were insufficient data comparing cladribine to other treatments for this outcome.

Table 9: Cognitive Decline

Comparator[a]	Natalizumab, RR (95% CI)	Cladribine, RR (95% CI)
Glatiramer acetate	–1.19 (–2.25 to –0.13)	NA
Interferon beta-1a	–1.09 (–2.13 to –0.04)	NA
Interferon beta-1b	–0.18 (–1.09 to 0.72)	NA
Teriflunomide	NA	NA
Dimethyl fumarate	NA	NA
Ocrelizumab	NA	NA
Ofatumumab	NA	NA

CI = confidence interval; NA = not available, RR = risk ratio.

[a]Only data for the treatments of interest to this review were extracted from the network meta-analysis netleague tables.

Source: Adapted with permission (CC BY-NC) from Gonzalez-Lorenzo et al. (2024), Appendix 10.[31]

Health-Related Quality of Life

Data on quality-of-life impairment in different studies were reported using different scales including non–MS-related quality-of-health questionnaires and MS-related questionnaires and subscales (physical and mental).

There were insufficient data that could be used in a network meta-analysis to compare natalizumab and cladribine with the other treatments of interest. Most of the evidence for quality of life is from comparisons with placebo in the pivotal trials of natalizumab and cladribine.

MS-Related Mortality

Data on mortality were available from 33 studies involving 34,500 participants with RRMS (94% of those included in the review) and assessing 16 treatments. Ten treatments assessed in 15 studies were compared with placebo, 13 treatments were evaluated in head-to-head comparisons in 15 studies, and 2 studies involving 2,751 participants had both a placebo and active treatment arm.

Using placebo as a common comparator, there was probably a trivial increase in the number of deaths in people treated with cladribine (OR = 0.98; 95% CI, 0.18 to 5.39) and a trivial increase in the number of deaths may have occurred in people treated with natalizumab (OR = 2.52; 95% CI, 0.12 to 52.69).

The network estimates of MS-related mortality are summarized in Table 10 for select treatments of interest:

- There was no difference between natalizumab and glatiramer acetate, interferon beta-1a, interferon beta-1b, teriflunomide, dimethyl fumarate, ocrelizumab, and ofatumumab in MS-related mortality rate.
- There was no difference between cladribine and glatiramer acetate, interferon beta-1a, interferon beta-1b, teriflunomide, dimethyl fumarate, ocrelizumab, and ofatumumab in MS-related mortality rate.

Table 10: MS-Related Mortality

Comparator[a]	Natalizumab, RR (95% CI)	Cladribine, RR (95% CI)
Glatiramer acetate	5.12 (0.17 to 156.95)	0.50 (0.05 to 5.09)
Interferon beta-1a	4.00 (0.15 to 106.34)	0.64 (0.08 to 5.25)
Interferon beta-1b	6.85 (0.11 to 414.99)	0.37 (0.01 to 9.58)
Teriflunomide	0.59 (0.01 to 26.33)	1.52 (0.09 to 25.92)
Dimethyl fumarate	3.37 (0.09 to 124.42)	0.76 (0.06 to 10.10)
Ocrelizumab	0.16 (0.00 to 7.68)	0.40 (0.02 to 7.82)
Ofatumumab	0.19 (0.00 to 27.85)	0.50 (0.01 to 35.96)

CI = confidence interval; RR = risk ratio.

[a]Only data for the treatments of interest to this review were extracted from the network meta-analysis netleague tables.

Source: Adapted with permission (CC BY-NC) from Gonzalez-Lorenzo et al. (2024), Appendix 13.[31]

Critical Appraisal of the Evidence

In the systematic review, Gonzalez-Lorenzo et al. used validated methods to assess risk of bias in individual studies using the Cochrane risk of bias tool. Risk of bias was appropriately assessed independently by 2 reviewers, with results detailed in a table of characteristics of included studies. Sensitivity analyses were

performed that included only trials with low risk of selection bias and attrition bias. Although this approach is methodologically sound, it was noted in the review that high prevalences (84% of trials high risk or unclear risk) of sponsor-related bias and performance bias (52% of trials high risk or unclear risk) across the included trials potentially impacted the validity of results.

Assumptions for network meta-analyses were tested and discussed. Gonzalez-Lorenzo et al. assessed heterogeneity, including heterogeneity within treatment comparisons and transitivity across treatment comparisons. Transitivity was assumed to hold based on similarities in eligibility criteria and outcome measures across studies. However, differences in patient or trial characteristics, especially with newer versus older trials, were acknowledged as potential hidden or unmeasured confounders that might influence treatment effects. Gonzalez-Lorenzo et al. stated there were no important differences identified across selected patient characteristics (such as age, disease duration, and baseline EDSS scores). Details about how patient and trial characteristics were examined and how it was determined that no important differences existed were not described.

Assessments of statistical heterogeneity for all direct pairwise comparisons and for the entire network were also performed. Additionally, statistical consistency was assessed by evaluating the agreement between direct and indirect estimates using 2 different approaches, including the design-by-treatment model to evaluate the assumption of consistency in the entire network.

Gonzalez-Lorenzo et al. did not find strong evidence of the presence of heterogeneity, either in direct pairwise comparisons or in the entire networks. They also found no substantial evidence of inconsistency. However, they acknowledged that the tests and approaches used, especially those to detect inconsistency, have limitations particularly for networks with few included studies for a given comparison.

It was noted in the review that sensitivity analyses based on including studies with only low risk of selection bias or attrition bias influenced the results for certain outcomes, but the differences compared with the base-case analysis were not substantial. Although Gonzalez-Lorenzo et al. concluded that the key assumptions of transitivity, heterogeneity, and consistency were reasonably met, there was suggestion that some factors may not have been accounted for in the analysis. Moreover, there was limited information provided about how decisions were made regarding the importance of these influences on results and differences between analyses.

The critical appraisal of the systematic review and network analysis included in this report was supplemented using A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) tool, an instrument used to assess the methodological quality of systematic reviews.[37] The systematic review and network meta-analysis scored high using the AMSTAR 2 checklist. A high AMSTAR 2 score indicates zero or 1 noncritical weakness; that is, the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question (Appendix 4).

Economic Evidence

The economic review consisted of a cost comparison for cladribine and natalizumab compared with other DMTs reimbursed for the first-line treatment of RRMS (i.e., glatiramer acetate, interferon beta-1a, interferon

beta-1b, ofatumumab, ocrelizumab, dimethyl fumarate, and teriflunomide). Additionally, a review of published and grey literature was conducted to identify relevant cost-effectiveness analyses.

CDA-AMC Analyses

The comparators presented in Table 11 have been deemed to be appropriate based on feedback received from clinical experts and drug plans. Recommended doses were based on each product's respective product monograph and validated by clinical experts. If discrepancies in dosing between the product monograph and Canadian clinical practice were noted, the dose specified by clinical experts was used. Pricing was based on publicly available list prices. As noted in the clinical review, 6 DMTs available in Canada are considered high-efficacy treatments by CMSWG: fingolimod, cladribine, natalizumab, alemtuzumab, ofatumumab, and ocrelizumab.[38] Because fingolimod and alemtuzumab are indicated for second-line use only, cladribine, natalizumab, ofatumumab, and ocrelizumab are referred to as high-efficacy treatments in the first line, and the remaining comparators (i.e., glatiramer acetate, interferon beta-1a, interferon beta-1b, dimethyl fumarate, and teriflunomide) are referred to as low-efficacy treatments.

Based on public list prices, cladribine and natalizumab are expected to be associated with an annual per patient cost of $44,968 and $46,750, respectively (Table 11). Comparator costs ranged from $5,449 to $48,867 per year for first-line treatments, with teriflunomide resulting in the lowest drug acquisition costs and peginterferon beta-1a resulting in the highest. Therefore, the incremental cost of cladribine ranged from $12,368 to $39,519 per patient annually compared with ocrelizumab and teriflunomide, respectively. When compared with peginterferon beta-1a, cladribine resulted in cost-savings of $3,899 per patient per year. Similarly, the incremental cost of natalizumab ranged from $14,150 to $41,301 per patient annually compared with ocrelizumab and teriflunomide, respectively. When compared with peginterferon beta-1a, natalizumab resulted in cost-savings of $2,116 per patient per year. As such, the reimbursement of cladribine and natalizumab for the treatment of RRMS is generally expected to increase overall drug acquisition costs for the treatment of RRMS in the first line of treatment.

Table 11: CDA-AMC Cost Comparison of First-Line Treatments for Relapsing-Remitting Multiple Sclerosis

Treatment	Strength	Form	Price ($)	Recommended dosage[a]	Daily cost ($)	Annual cost ($)
Cladribine (Mavenclad)	**10 mg**	**Tablet**	**3,212.0000[b]**	**1.75 mg/kg body weight per year taken over 2 weeks, for 2 years[c]**	**123.20**	**44,968**
Natalizumab (Tysabri)	**300 mg/15 mL**	**Single-use vial**	**3,596.1729[b]**	**300 mg every 4 weeks**	**128.08**	**46,750**
Injectable therapies						
Glatiramer acetate (generic)	20 mg/1 mL	Prefilled syringe	27.8587	20 mg daily	27.86	10,168
Interferon beta-1a (Avonex)	30 mcg/0.5 mL	Prefilled syringe, prefilled autoinjector pen	491.2525[b]	30 mcg weekly	69.99	25,545
Interferon beta-1a (Rebif)	0.22 mcg/0.5 mL 44 mcg/0.5 mL	Prefilled syringe, cartridge, or pen	170.6067[b] 207.7000[b]	44 mcg 3 times a week; dose can be reduced to 22 mcg 3 times weekly if higher dose cannot be tolerated	72.92 to 88.77	26,615 to 32,401
Peginterferon beta-1a (Plegridy)	63 mcg/0.5mL 94 mcg/0.5mL 125 mcg/0.5 mL	Prefilled syringe or pen	1,879.4900[b]	SC injection every 2 weeks • dose 1: 63 mcg • dose 2: 94 mcg • dose 3 and thereafter: 125 mcg	133.88	48,867
Interferon beta-1b (Betaseron)	0.3 mg	Single-use vial	110.0000[b]	0.25 mg every other day	55.00	20,075
Ofatumumab (Kesimpta)	20 mg/0.4 mL	Prefilled syringe, Sensoready pen	2,318.7400[b]	20 mg at weeks 0, 1, and 2 followed by subsequent monthly dosing of 20 mg, starting at week 4	Daily average: Year 1: 95.29 Year 2: 76.23	Year 1: 34,781 Year 2: 27,825
Infusion therapies						
Ocrelizumab (Ocrevus)	300 mg/10 mL	Single-use vial	8,150.0000[b]	600 mg every 6 months[d]	89.32	32,600

Treatment	Strength	Form	Price ($)	Recommended dosage[a]	Daily cost ($)	Annual cost ($)
Oral therapies						
Dimethyl fumarate (generic)	120 mg 240 mg	Delayed-release capsule	4.4266 8.6888	120 mg twice daily for first 7 days then 240 mg twice daily thereafter	Daily average: Year 1: 17.07 Year 2: 17.38	Year 1: 6,230 Year 2: 6,343
Teriflunomide (generic)	14 mg	Tablet	14.9300	14 mg daily	14.93	5,449

CDA-AMC = Canada's Drug Agency; SC = subcutaneous.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed October 2024),[39] unless otherwise indicated, and do not include dispensing fees. Annual costs based on 365 days per year.

[a]Recommended doses from the appropriate product monographs unless otherwise indicated.

[b]Treatment cost derived from Exceptional Access Program (accessed October 2024).[40]

[c]The total dose per patient annually is divided as 2 treatment courses: 1 at the beginning of the first month and the next at the beginning of the second month of the respective year. Each treatment week consists of 10 mg to 20 mg as a single daily dose. For example, a patient weighing 70 kg would take 7 tablets in treatment weeks 1 and 2 for both year 1 and 2 of the treatment course (14 tablets annually).

[d]The initial 600-mg dose of ocrelizumab is administered as 2 separate IV infusions: a 300-mg infusion followed 2 weeks later by a second 300-mg infusion. Subsequent doses are administered as single 600-mg IV infusions every 6 months.

Cladribine and natalizumab are currently reimbursed as second-line treatments for RRMS (i.e., after failure or documented intolerance to a previous DMT).[41] The purpose of this review was to examine the comparative costs and effects of cladribine or natalizumab if they were to be reimbursed in the first line of treatment. Clinical experts indicated that the primary reasons for patients to switch from a first-line to a second-line treatment include tolerability concerns, AEs and poor treatment effects, and/or loss of treatment effect. In addition to the multiple reasons for treatment switching, clinical experts indicated that multiple factors would be used to evaluate treatment effect which could lead to treatment switching. For example, the occurrence of a single relapse on a first-line treatment may not be a sufficient reason to switch treatments, but this is dependent on which treatment the patient is receiving. According to the clinical review, no direct or indirect comparative evidence was identified to estimate the duration of treatment with first-line therapies. Additionally, no evidence was identified in a DMT-naive population to estimate failure rates of first-line treatments for patients with RRMS. As such, there is insufficient clinical evidence to evaluate the comparative time spent on first-line therapies, or their respective failure rates, to estimate overall treatment costs by first-line therapy and accounting for subsequent therapies.

When considering the cost consequences of reimbursing natalizumab and cladribine in the first-line setting, consideration was also given to how this impacts subsequent therapy costs when patients do move on to receive subsequent treatments. To estimate potential subsequent therapy costs, CDA-AMC elicited expert opinion on the expected distribution of patients across possible second-line treatments based on which treatment they received in the first line (Appendix 5, Table 17). The annual costs for second-line treatments in Table 12 were estimated by multiplying the expected distribution of patients across second-line treatments by their first-line treatment (Appendix 5, Table 17) and then by each second-line treatment's annual cost (Table 11 and Appendix 5, Table 16).

Overall, the costing exercise demonstrates that, upon requiring a second-line therapy, annual costs are expected to be similar regardless of the treatment the patient had received prior. If cladribine were reimbursed as a first-line treatment, the annual cost of second-line treatments may be slightly lower than other first-line treatments. This is based on the expert opinion that those who received cladribine as first-line therapy are more likely to receive lower-cost drugs (i.e., dimethyl fumarate and teriflunomide) as second-line treatments.

This exercise has several limitations, most notably that patient distributions across second-line treatments were informed by clinical expert opinion and may not be reflective of actual clinical practice in Canada. Second, it does not account for time spent on each line of therapy. For example, although teriflunomide has the lowest cost in the first-line setting, if patients move quickly to second-line therapy, then the cost of the total treatment pathway may be higher than starting on a higher-cost first-line therapy. A more appropriate analysis would have captured the expected treatment switching rate by first-line treatment (accounting for all causes of treatment switching; i.e., intolerance and lack of treatment response), and expected time spent on each line of therapy. However, this was not possible due to the lack of available clinical evidence to parameterize such an analysis.

Table 12: Annual Costs of Treatment by Line of Therapy

Treatment	Annual costs (first line)	Annual costs (second line)[a]
Glatiramer acetate	$10,168	$32,787
Interferon beta-1a	$33,357	$33,287
Interferon beta-1b	$20,075	$33,287
Teriflunomide	$5,449	$33,287
Dimethyl fumarate	$6,286	$33,148
Ocrelizumab	$32,600	$34,572
Ofatumumab	$31,303	$38,001
Natalizumab	$46,750	$32,928
Cladribine	$44,968	$28,735

Notes: If annual drug costs were a range, the average of the range was used to determine annual costs.

Although alemtuzumab and fingolimod are not included as first-line treatment options, they were included in the distribution of options patients could receive as second-line treatments.

[a]Estimated by multiplying the expected distribution of patients across second-line treatments by their first-line treatment and then by the annual cost of the second-line treatment.

Other Economic Evidence

No Canadian cost-effectiveness analyses were identified in a literature search conducted November 28, 2024. However, the review of the literature identified several relevant publications that provided key information on the treatment of RRMS (Appendix 5, Table 18).

As noted in the challenges and limitations section, none of the literature identified accurately represented the decision problem of this review. Specifically, the identified literature either did not represent the target population for this review (i.e., DMT-naive RRMS), did not include all relevant Canadian comparators, or did not consider subsequent lines of therapy in its analysis. Because treatment sequencing is key to the decision problem of this review, none of the available literature could adequately inform cost-effectiveness of moving natalizumab and cladribine from second line of therapy to first line.

One study examined the health benefits and costs associated with early highly effective treatment strategy compared with an escalation treatment strategy.[42] Early highly effective treatments included starting with cladribine, ocrelizumab, ofatumumab, or natalizumab as first-line treatment, followed by other high-efficacy DMTs. Findings suggested the most cost-effective early highly effective treatment sequence was ocrelizumab followed by cladribine, natalizumab, and alemtuzumab. Limitations of this study included that the network meta-analysis informing the treatment efficacy assumed DMT efficacy to be constant regardless of the line of treatment used in, and naive comparisons were used to inform the probabilities of treatment switching due to AEs.

As noted in the CADTH Health Technology Review for alemtuzumab, cladribine, fingolimod, and natalizumab for first-line treatment in adult patients with highly active RRMS, there was a lack of evidence to support a cost-utility analysis of these treatments for highly active RRMS.[19] Therefore, the comparative cost-effectiveness of first-line treatments for highly active RRMS is unknown as is the cost-effectiveness of

moving natalizumab and cladribine from second line to first line in highly active RRMS. Note the population of the previous Health Technology Review was narrower than the population for this current review but was aligned with the initial scope of the current review (i.e., highly active RRMS).

Issues for Consideration

- Based on the clinical review conclusions, the NMA showed that cladribine and natalizumab are more effective than all but 1 of the lower-efficacy DMTs of interest in reducing the frequency of relapses over 2 years of treatment. There were no data to determine comparative efficacy of natalizumab and cladribine compared with 2 high-efficacy DMTs (ocrelizumab and ofatumumab) for preventing relapses over 2 years.
- Currently, 2 generic cladribine submissions are under review with Health Canada.[43] Should any or both of these submissions receive regulatory approval and become available in Canada, the cost of cladribine would be lower than estimated in this review. According to the pan-Canadian Pharmaceutical Alliance Tiered Pricing Framework, the price of a single-source generic product would be reduced to 55% of the brand reference after 3 months of funding.[44] Therefore, should generic cladribine become available in Canada, the cost per 10-mg tablet could decrease to $1,445.40, corresponding to a cost of $20,236 per patient per year.
- Health Canada currently lists a biosimilar natalizumab submission under review.[45] Should this submission receive regulatory approval, and if biosimilars to natalizumab are considered clinically equivalent to natalizumab and become available in Canada, the cost of natalizumab may be lower than what was estimated in this review.
- Natalizumab was reviewed by CADTH in 2009 and received a recommendation of reimburse with clinical conditions.[25] Reimbursement was exclusive to patients who trialled at least 2 DMTs and had increased T2 lesion load compared with previous MRI or at least 1 gadolinium-enhancing lesion, and 2 or more disabling relapses in the previous year.
- Cladribine was reviewed by CADTH in 2017 and received a recommendation of reimburse with clinical conditions.[30] Reimbursement was exclusive to patients who trialled 1 previous therapy for RRMS and who had at least 1 relapse in the past 12 months. Reimbursement was conditional on a price reduction.
- No Canadian cost-effectiveness studies were identified based on a literature search conducted on November 28, 2024. Relevant grey and published literature are summarized in Table 18.

Discussion

Summary of the Input and Evidence

Input from patient organizations and clinician groups highlighted the need for a broader spectrum of high-efficacy first-line treatments for RRMS. Importantly, there is an unmet need for DMTs with different mechanisms of action and modes of administration to address the heterogeneity of patient characteristics, disease presentation, and treatment response in RRMS. The inputs from patient organizations and clinician groups noted that high-efficacy treatments have been consistently shown to lead to better outcomes in

RRMS, and cited clinical practice guidelines recommending initiation of treatment with a high-efficacy DMT in most patients, particularly those who present with high disease activity.[5,46] Yet, although the understanding of the disease pathophysiology and the optimal management of RRMS have substantially evolved, the patient organizations and clinician groups asserted that current drug reimbursement policy in Canada has not evolved with it. People living with MS are rarely allowed to initiate treatment with a high-efficacy therapy, which requires clinicians to follow the traditional escalation approach before enabling access to high-efficacy treatments. The patient and clinician groups highlighted that further delays in providing access to high-efficacy treatments in first line continue to have a negative impact on patients' lives, including faster functional decline and permanent disability.

Based on the high certainty of the evidence highlighted in the systematic review, it appears natalizumab and cladribine may be more effective for preventing clinical relapses in the short term (generally 24 months or less) and have similar harms compared with other DMTs used in first-line treatment of RRMS except ocrelizumab and ofatumumab. For preventing disability from worsening in the short term, natalizumab is more effective than several other treatments based on moderate certainty of evidence. Natalizumab and cladribine were more effective than all the lower-efficacy DMTs of interest, except dimethyl fumarate, for preventing relapses over 24 months. Regarding safety, the number of people who experienced SAEs or discontinued treatment due to AEs was similar for all the treatments considered. These results are supported by other studies including RCTs, and observational studies that have demonstrated a benefit of early intensive treatment strategy in reducing relapses and disability over time.[11,47] However, the comparative safety and costs of early intensive versus escalating strategies have been less extensively studied. A recent systematic review of early intensive treatment versus escalation strategies suggests that the early intensive treatment strategy was more effective in preventing EDSS worsening, without an increased proportion of SAEs or costs, based on data from the UK.[48]

Health Canada regulatory approval for natalizumab and cladribine placed them for second-line or later-line use for the treatment of patients with RRMS and was based on the benefit-risk ratio determined from the observations in the pivotal trials of the 2 drugs. DMTs for RRMS are associated with specific harms related to their mechanism of action. For cladribine, Health Canada expressed concern about the higher proportion of patients treated with cladribine in the CLARITY trial who experienced certain notable AEs, such as lymphopenia, herpes zoster infection, and neoplasms compared with placebo. As a result, Health Canada's benefit-risk evaluation for cladribine was that it should generally not be used as a first-line drug in the treatment of RRMS. For natalizumab, Health Canada considers the benefit-risk profile is favourable as monotherapy for the treatment of RRMS, but states that it is generally recommended for patients with MS who have had an inadequate response to, or are unable to tolerate, other therapies for MS. Treatment with natalizumab has been associated with an increased risk of PML, which can cause disability or death. Concern for severe adverse effects in high-efficacy drugs, including natalizumab and cladribine, has been a drawback in the early initiation strategy and influenced reimbursement criteria that put restrictions on their use. The original CADTH-recommended reimbursement criteria for these 2 drugs limited reimbursement to later lines after treatment with drugs traditionally considered to have a better safety profile. However, the initial concern over the safety of these 2 drugs may be eased by current evidence, including from the network

meta-analysis included in this report, showing similar rates of SAEs among most DMTs. Many of the patients on lower-efficacy first-line drugs will eventually require escalation of therapy to higher-efficacy therapies due to suboptimal response.[49] Therefore, any risk of these AEs in an individual may simply be postponed. The clinical experts consulted for this review noted that these risks, including risk of PML, are now mitigated with higher clinician awareness, risk-mitigation programs implemented by the sponsors, and availability of biomarkers for early monitoring, which was not the case when natalizumab was initially evaluated in clinical trials. In addition, there is some evidence that extended interval dosing (every 5 to 8 weeks) is associated with lower risk of PML. The clinical experts emphasized that several factors and strategies, including vaccination, John Cunningham virus monitoring, and screening for infectious diseases, have significantly reduced the risk of SAEs with natalizumab and cladribine. Because of this, in the experts' opinions, the only barrier to using these treatments for patients who are thought to benefit from either drug and who have no contraindications is reimbursement restrictions not safety concerns.

Natalizumab — in addition to being a highly effective DMT — is considered by the clinical experts consulted by CDA-AMC to have a rapid onset of action (faster than both ocrelizumab and ofatumumab). Therefore, it may be a better treatment option for patients with high disease activity (e.g., multiple gadolinium-enhancing lesions or multiple relapses within a year). The clinical experts identified an unmet need for a high-efficacy DMT with a fast onset of action for use in patients with high disease activity who would benefit from rapid stabilization, particularly those with certain comorbidities, such as inflammatory bowel disease which may be exacerbated by B cell–directed therapy (i.e., ocrelizumab and ofatumumab). Natalizumab may fill this unmet need; however, the reviewed network meta-analysis did not examine comparative treatment differences related to onset of effects. As well, no subgroup analyses by disease severity or rate of progression were possible because of the already mentioned limitations in the evidence base in this regard.

Cladribine offers a different safety profile relative to other DMTs for RRMS. Cladribine does not entail continuous immunosuppression, so the risk of infection is not as high as with some DMTs. It may also be preferred for use in patients who are planning to become pregnant and for older patients. It may be more suitable for patients who are planning to become pregnant because the maximum recommended treatment duration is 2 years per the product monograph, allowing for a treatment-free period that is more favourable for pregnancy planning. Cladribine is an orally administered DMT. As such, it would be suitable for patients who have difficulty with needles or IV infusions and would provide these patients with a higher-efficacy option in first line. These factors related to treatment with cladribine were highlighted by patient groups and clinicians in their input to CDA-AMC related to this review.

Limitations of the Evidence

The reviewed network meta-analysis has a few limitations related to the included trials and as it relates to the scope of this report. First, the patient population of the included trials was a mix of both patients who had not been previously treated with a DMT and those previously treated with DMTs. The cladribine CLARITY trial was reported as including a mixed population of patients with and without previous treatment, while the natalizumab AFFIRM trial did not report data about previous treatments with DMTs. Therefore, generalizability of the results strictly to a population with no history of DMT use may be limited. Second,

most of the included treatments were evaluated in few trials; data for both natalizumab and cladribine came from only 1 RCT each. Third, the efficacy of all the treatments beyond 2 years is uncertain, with only 4 of the 50 included studies contributing to 36 months of treatment duration. This is particularly important with a chronic neurological disease such as MS, which often requires longer follow-up to observe treatment benefits and typically requires lifelong treatment. Fourth, shorter-term trials provide limited safety data and may not provide a reliable risk profile of treatments, especially for less common adverse effects. Finally, there were insufficient data for some outcomes in the trials, including health-related quality of life and symptoms, and treatment comparisons were limited. This was partly due to the inability to pool data from different trials that had used different definitions for these outcome measures.

Conclusions and Implications for Policy

RRMS is a rapidly changing therapeutic landscape requiring complex decision-making to optimize treatment based on the needs of the individual patients as they evolve during the clinical course. Patients and clinicians are interested in access to a wider range of DMTs and flexibility of choice of therapy for a personalized treatment approach to optimize patient outcomes. There is evidence to suggest that treatment with high-efficacy DMTs in first line improves patient outcomes compared with escalating from lower-efficacy drugs. However, there are currently only 2 high-efficacy DMTs that are publicly reimbursed for upfront treatment of RRMS; both have the same mechanism of action and neither is an oral medication. Evidence from the most comprehensive network meta-analysis to date on the efficacy and safety of DMTs for RRMS suggests that both natalizumab and cladribine are more effective for preventing relapses at 2 years than almost all currently reimbursed low-efficacy drugs that are required to be trialled initially. Importantly, neither natalizumab nor cladribine were less favourable with respect to commonly reported SAEs than all treatment comparators, including both lower-efficacy and high-efficacy first-line treatments.

This streamlined drug review integrates extensive input from patient groups and clinicians with best available evidence and provides a robust synthesis of clinical trial data on the efficacy and safety of treatments for RRMS. The findings support use of natalizumab and cladribine as alternative high-efficacy treatments of RRMS in the first line of treatment. This would align reimbursement with emerging best clinical practice with a shift to early intensive treatment as the new standard care for patients with RRMS.

The reimbursement of cladribine and natalizumab as first-line treatments for RRMS is expected to increase overall drug acquisition costs compared with all other first-line treatments reimbursed for RRMS except for peginterferon beta-1a. Based on the clinical review, although there were studies included in the network meta-analysis that included patients who had not been previously treated with a DMT, the network meta-analysis evidence is from a mixed population of both those with and without DMT experience. Because the evidence was from a mixed population, no literature on a population exclusively with no history of DMT use was available to estimate the comparative effectiveness of cladribine and natalizumab in the first line of treatment compared with other treatments available in the first line. However, given the totality of the evidence, cladribine and natalizumab were considered more effective than low-efficacy DMTs (glatiramer acetate, interferon beta-1a, interferon beta-1b, dimethyl fumarate, and teriflunomide) and as effective as high-efficacy DMTs (ocrelizumab and ofatumumab) for some outcomes. Currently, ofatumumab and

ocrelizumab are the only high-efficacy DMTs reimbursed in the first-line setting in Canada. Compared with these therapies, cladribine and natalizumab have higher annual treatment costs using public list prices. Looking at the full treatment pathway, if a patient requires a further line of therapy, subsequent treatment costs may be similar or slightly lower for those who receive cladribine or natalizumab up front. Therefore, if the cost of natalizumab or cladribine does not exceed that of ofatumumab or ocrelizumab, it would likely be considered cost-effective relative to these therapies. Compared with low-efficacy DMTs, their cost-effectiveness is uncertain in the absence of evidence.

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Appendix 1: Literature Search Strategy

Please note that this appendix has not been copy-edited.

Clinical Literature Search

Overview

Interface: Ovid

Databases:

- MEDLINE All (1946 to present)
- Embase (1974 to present)

Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: September 20, 2024

Alerts: Monthly search updates until project completion

Search filters applied: Systematic reviews; meta-analyses; network meta-analyses; health technology assessments; guidelines; overview of reviews.

Table 13: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*****	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for 1 or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.rn	Registry number

Syntax	Description
.nm	Name of substance word (MEDLINE)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Warning

To conduct a comprehensive search, antiquated, noninclusive, or potentially stigmatizing terms may have been included that may have appeared in past and present literature. CDA-AMC recognizes and acknowledges the inappropriate and harmful nature of terms that may appear in search strategies and include this warning so the reader can determine how they would like to proceed.

The warning is modified from the University of Michigan Library's guidance, Addressing antiquated, non-standard, exclusionary, and potentially offensive terms in evidence syntheses and systematic searches.

Multidatabase Strategy

1. Natalizumab/
2. (natalizumab* or tysabri* or antegren* or HSDB8174 or HSDB-8174 or an100226 or an-100226 or bg0002 or bg-0002 or dst356a1 or dst-356al or pb006 or pb-006).ti,ab,kf,ot,hw,rn,nm.
3. Cladribine/
4. (cladribin* or cladarabin* or biodribin* or intocel* or leustat* or litak* or litax* or mavenclad* or movectro* or mylinax* or BRN0624220 or BRN-0624220 or CCRIS9374 or CCRIS-9374 or HSDB7564 or HSDB-7564 or NSC105014* or NSC-105014* or RWJ26251 or RWJ-26251).ti,ab,kf,ot,hw,rn,nm.
5. or/1-4
6. Multiple Sclerosis, Relapsing-Remitting/
7. (RRMS or RMS).ti,ab,kf.
8. ((ms or multiple scleros*) adj3 (relaps* or remit*)).ti,ab,kf.
9. or/6-8
10. 5 and 9
11. 10 use medall
12. *natalizumab/
13. (natalizumab* or tysabri* or antegren* or HSDB8174 or HSDB-8174 or an100226 or an-100226 or bg0002 or bg-0002 or dst356a1 or dst-356al or pb006 or pb-006).ti,ab,kf,dq.
14. *cladribine/
15. (cladribin* or cladarabin* or biodribin* or intocel* or leustat* or litak* or litax* or mavenclad* or movectro* or mylinax* or BRN0624220 or BRN-0624220 or CCRIS9374 or CCRIS-9374 or

HSDB7564 or HSDB-7564 or NSC105014* or NSC-105014* or RWJ26251 or RWJ-26251).ti,ab,kf,dq.

16. or/12-15
17. exp Multiple sclerosis/ and (relapse/ or remission/ or (relaps* or remit*).ti,ab,kf,dq.)
18. (RRMS or RMS).ti,ab,kf.
19. ((ms or multiple scleros*) adj3 (relaps* or remit*)).ti,ab,kf.
20. or/17-19
21. 16 and 20
22. 21 use oemezd
23. 11 or 22
24. (systematic review or meta-analysis).pt.
25. meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or “meta analysis (topic)”/ or “systematic review (topic)”/ or exp technology assessment, biomedical/ or network meta-analysis/
26. ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf.
27. ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.
28. ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.
29. (data synthes* or data extraction* or data abstraction*).ti,ab,kf.
30. (handsearch* or hand search*).ti,ab,kf.
31. (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.
32. (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.
33. (meta regression* or metaregression*).ti,ab,kf.
34. (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
35. (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
36. (cochrane or (health adj2 technology assessment) or evidence report).jw.
37. (comparative adj3 (efficacy or effectiveness)).ti,ab,kf.
38. (outcomes research or relative effectiveness).ti,ab,kf.
39. ((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.
40. [(meta-analysis or systematic review).md.]
41. (multi* adj3 treatment adj3 comparison*).ti,ab,kf.
42. (mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.

43. umbrella review*.ti,ab,kf.
44. (multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.
45. (multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.
46. (multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.
47. or/24-46
48. 23 and 47
49. remove duplicates from 48

Grey Literature

Search dates: September 20 to 23, 2024

Keywords: Natalizumab, cladribine, multiple sclerosis

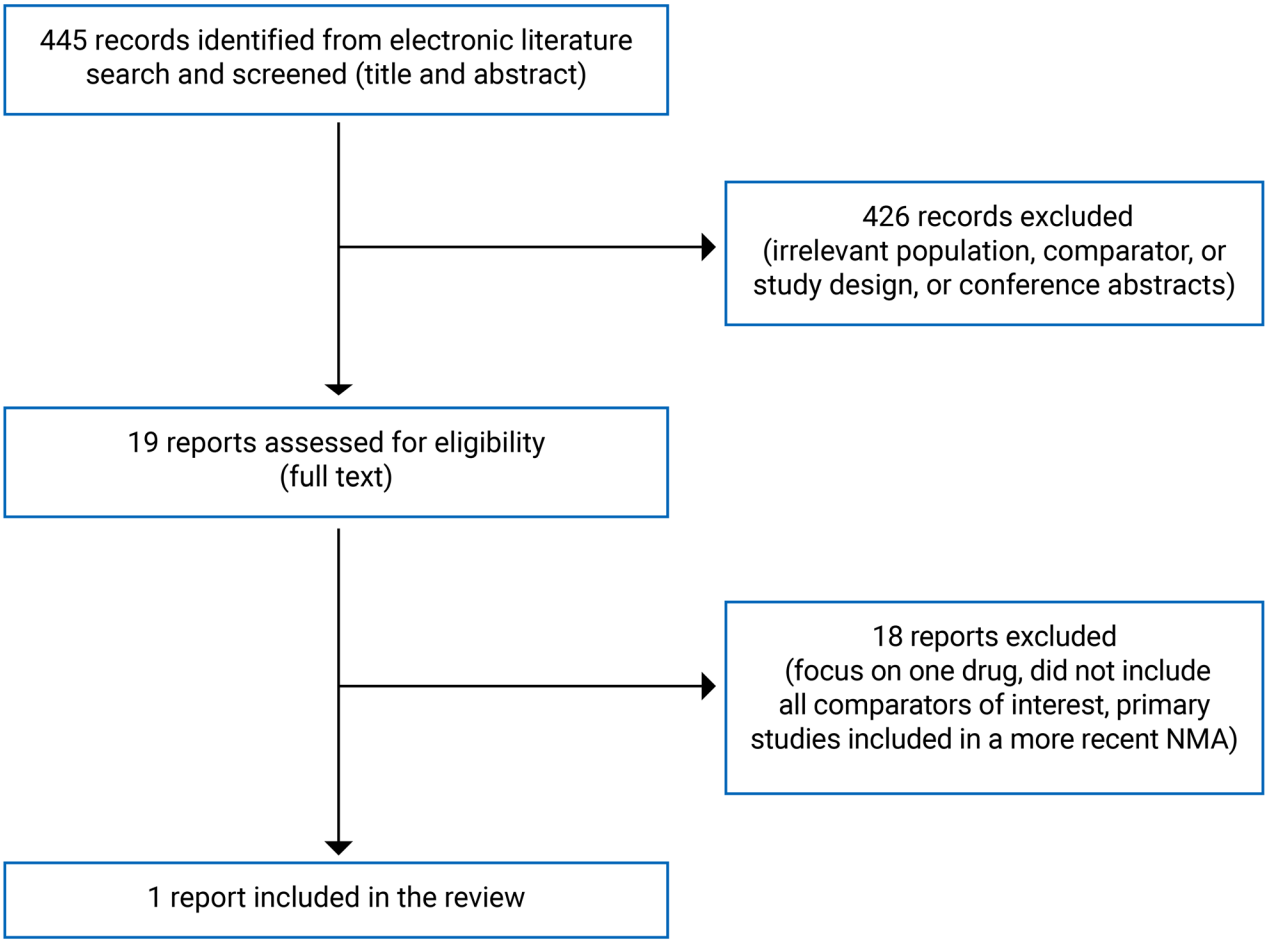
Relevant websites from the following sections of the grey literature checklist Grey Matters: A Practical Tool for Searching Health-Related Grey Literature were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Health Statistics
- Internet Search
- Open Access Journals

Appendix 2: Selection of Included Studies

Please note that this appendix has not been copy-edited.

Figure 2: PRISMA Flow Chart of Selected Reports



Appendix 3: List of Excluded Studies

Please note that this appendix has not been copy-edited.

Table 14: List of Excluded Studies

Study	Number of RCTs included	Treatments compared	Funding	Reason for exclusion
Samjoo, et al. (2023)[50]	41	Ublituximab, alemtuzumab, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, interferon beta-1a, interferon beta-1a 30 mcg intramuscular; interferon beta-1a 44 mcg subcutaneous, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, teriflunomide	Industry	More recent NMA available Focus on ublituximab
Pipek, et al. (2023)[48]	7	Natalizumab, rituximab, alemtuzumab, cladribine, ocrelizumab	None	Overview of early intensive vs escalating strategies
Sladowska, et al. (2022)[51]	33	natalizumab, fingolimod, alemtuzumab, cladribine, ocrelizumab, ofatumumab, ozanimod, as well as a potentially high-efficacy DMT, ponesimod,	Academic	More recent NMA available
Drudge, et al. (2022)[52]	4	Ofatumumab, natalizumab, fingolimod, dimethyl fumarate	Industry	Japanese patient population
Bose, et al. (2022)[53]	26	glatiramer acetate, interferon beta-1a, pegylated interferon beta-1a, natalizumab, cladribine, fingolimod, teriflunomide, dimethyl fumarate, ocrelizumab, ozanimod, and mitoxantrone	Not reported	More recent NMA available
Liu, et al. (2021)[54]	21	glatiramer acetate, natalizumab, cladribine, fingolimod, teriflunomide, laquinimod, alemtuzumab, dimethyl fumarate, ocrelizumab, ozanimod, ofatumumab	None	More recent NMA available
Bartosik-Psujek, et al. (2021)[55]	6	Cladribine, fingolimod, dimethyl fumarate, teriflunomide	Industry	Focus on cladribine tablets with other oral DMTs Focus on 1 outcome (no evidence of disease activity NEDA)

Study	Number of RCTs included	Treatments compared	Funding	Reason for exclusion
Li, et al. (2020)[56]	23	alemtuzumab, ocrelizumab, mitoxantrone, natalizumab, fingolimod, peginterferon beta-dimethyl fumarate, teriflunomide glatiramer acetate, interferon beta-1a, interferon beta-1b, teriflunomide	None	More recent NMA available
Landmeyer, et al. (2020)[57]	44 (41 in NMA)	Beta-interferon, glatiramer acetate, mitoxantrone, natalizumab, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, cyclophosphamide, laquinimod, daclizumab, ocrelizumab, cladribine, azathioprine, rituximab, and ozanimod	None	Focus on cognition
Giovannoni, et al. (2020)[58]	33	alemtuzumab, natalizumab, ocrelizumab, cladribine, fingolimod, dimethyl fumarate, PEG INF beta 1a, glatiramer acetate, interferon beta-1b, interferon beta-1a, teriflunomide	Industry	More recent NMA available
Xu, et al. (2018)[59]	14	natalizumab, natalizumab plus interferon beta-1a, alemtuzumab, daclizumab, and ocrelizumab, interferon beta-1a, teriflunomide	Academic	Focus on monoclonal antibodies
Siddiqui, et al. (2018)[60]	44	alemtuzumab, cladribine, daclizumab, dimethyl fumarate, fingolimod, glatiramer acetate, interferon beta-1a, interferon beta-1b, PEG interferon beta-1a, natalizumab, ocrelizumab, teriflunomide	Industry	More recent NMA available Focus on cladribine
Lucchetta, et al. (2018)[61]	33	alemtuzumab, azathioprine, cladribine, daclizumab, dimethyl fumarate, fingolimod, glatiramer acetate, interferon beta-1a, natalizumab, ocrelizumab, rituximab, teriflunomide	Academic	More recent NMA available
Hamidi, et al. (2018)[62]	37	Alemtuzumab, dimethyl fumarate, fingolimod, glatiramer acetate, interferon beta-1a (Avonex), interferon beta-1a (Rebif), interferon beta-1b (Betaferon), interferon beta-1b (Extavia), natalizumab, peg--	Academic	More recent NMA available

Study	Number of RCTs included	Treatments compared	Funding	Reason for exclusion
		interferon beta-1a (Plegridy), teriflunomide		
Tramacere, et al. (2015)[32]	39	Immunoglobulins, fingolimod, natalizumab, glatiramer acetate, teriflunomide, ocrelizumab, pegylated interferon beta-1a, alemtuzumab, daclizumab, laquinimod, interferon beta-1a, interferon beta-1b, mitoxantrone, azathioprine, dimethyl fumarate	Academic (Cochrane)	Does not include all comparators of interest More recent NMA available
Hutchinson, et al. (2014)[63]	27	Dimethyl fumarate, interferon beta-1a, interferon beta-1b, glatiramer acetate, fingolimod, natalizumab, and teriflunomide	Industry	Does not include all comparators of interest More recent NMA available
Hadjigeorgiou, et al. (2013)[64]	48	Betaferon 250mcg, Avonex 30mcg, Rebif 44mcg, Rebif 22mcg, Aubagio 7 mg, Aubagio 14 mg, Copaxone 20 mg, Tysabri 300 mg, Gilenya 0.5 mg and Novantrone	None	Does not include all comparators of interest. More recent NMA available
Filippini, et al. (2013)[65]	44	interferon beta□1b, interferon beta□1a, glatiramer acetate, natalizumab, mitoxantrone, methotrexate, cyclophosphamide, azathioprine, IV immunoglobulins, and long□term corticosteroids	Academic (Cochrane)	More recent NMA available

Appendix 4: Critical Appraisal of the Included Study

Please note that this appendix has not been copy-edited.

Table 15: AMSTAR 2 — A Critical Appraisal Tool for Systematic Reviews That Include Randomized and/or Nonrandomized Studies of Health Care Interventions[37]

Item to check	Item to check	Yes or no
1. Did the research questions and inclusion criteria for the review include the components of PICO?		
For Yes: • Population • Intervention • Comparator group • Outcome	Optional (recommended) • Time frame for follow-up	**Yes** No
2. Did the report of the review contain an explicit statement that the review methods were established before the conduct of the review and did the report justify any significant deviations from the protocol?		
For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: • review question(s) • a search strategy • inclusion/exclusion criteria • a risk of bias assessment	For Yes: As for partial yes, plus the protocol should be registered and should also have specified: • a meta-analysis/synthesis plan, if appropriate, and • a plan for investigating causes of heterogeneity • justification for any deviations from the protocol	**Yes** Partial Yes No
3. Did the review authors explain their selection of the study designs for inclusion in the review?		
For Yes, the review should satisfy ONE of the following: • Explanation for including only RCTs • OR explanation for including only NRSI • OR explanation for including only RCTs and NRSI	—	**Yes** No
4. Did the review authors use a comprehensive literature search strategy?		
• searched at least 2 databases (relevant to research question) • provided keyword and/or search strategy • justified publication restrictions (e.g., language)	For Yes, should also have (all the following): • searched the reference lists / bibliographies of included studies • searched trial/study registries • included/consulted content experts in the field • where relevant, searched for grey literature • conducted search within 24 months of completion of the review	**Yes** Partial Yes No
5. Did the review authors perform study selection in duplicate?		
For Yes, either ONE of the following: • at least 2 reviewers independently agreed on selection of eligible studies and achieved	—	**Yes** No

Item to check	Item to check	Yes or no
consensus on which studies to include • OR 2 reviewers selected a sample of eligible studies **and** achieved good agreement (at least 80%), with the remainder selected by one reviewer.		
6. Did the review authors perform data extraction in duplicate?		
For Yes, either ONE of the following: • at least 2 reviewers achieved consensus on which data to extract from included studies • OR 2 reviewers extracted data from a sample of eligible studies **and** achieved good agreement (at least 80%), with the remainder extracted by one reviewer.	—	**Yes** No
7. Did the review authors provide a list of excluded studies and justify the exclusions?		
For Partial Yes: • provided a list of all potentially relevant studies that were read in full-text form but excluded from the review	For Yes, must also have: • Justified the exclusion from the review of each potentially relevant study	**Yes** Partial Yes No
8. Did the review authors describe the included studies in adequate detail?		
For Partial Yes (ALL the following): • described populations • described interventions • described comparators • described outcomes • described research designs	For Yes, should also have ALL the following: • described population in detail • described intervention in detail (including doses where relevant) • described comparator in detail (including doses where relevant) • described study's setting • time frame for follow-up	**Yes** Partial Yes No
9. The review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?		
RCTs For Partial Yes, must have assessed RoB from: • unconcealed allocation, and • lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	For Yes, must also have assessed RoB from: • allocation sequence that was not truly random, and • selection of the reported result from among multiple measurements or analyses of a specified outcome	**Yes** Partial Yes No Includes only NRSI
NRSI For Partial Yes, must have assessed RoB: • from confounding, and • from selection bias	For Yes, must also have assessed RoB: • methods used to ascertain exposures and outcomes, and • selection of the reported result from among multiple measurements or analyses of a specified outcome	Yes Partial Yes No Includes only RCTs

Item to check	Item to check	Yes or no
10. Did the review authors report on the sources of funding for the studies included in the review?		
For Yes • Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies		**Yes** No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?		

RCTs
For Yes:
• The authors justified combining the data in a meta-analysis
  ◦ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
  ◦ AND investigated the causes of any heterogeneity
		Yes
		No
		No meta-analysis conducted

For NRSI
For Yes:
• The authors justified combining the data in a meta-analysis
  ◦ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
  ◦ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
  ◦ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review
		Yes
		No
		No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?		
For Yes: • included only low risk of bias RCTs • OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.		**Yes** No No meta-analysis conducted
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?		
For Yes: • included only low risk of bias RCTs • OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results		**Yes** No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?		
For Yes: • There was no significant heterogeneity in the results • OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review		**Yes** No

Item to check	Item to check	Yes or no
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?		
For Yes: ● performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias		**Yes** No No meta-analysis conducted
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?		
For Yes: ● The authors reported no competing interests OR ● The authors described their funding sources and how they managed potential conflicts of interest		**Yes** No

Appendix 5: Economic Analyses

Table 16: CDA-AMC Cost Comparison of Second-Line Treatments for Relapsing-Remitting Multiple Sclerosis

Treatment	Strength	Form	Price ($)	Recommended dosage[a]	Daily cost ($)
Alemtuzumab (Lemtrada)	12 mg/1.2 mL	Single-use vial	1,085.9258[b] per mg	12 mg/day for 5 days followed by 12 mg/day for 3 days 12 months after first initial treatment course	Daily average, Year 1: 178.51; Year 2: 107.11
Fingolimod (generic)	0.5 mg	Capsule	73.9096	0.5 mg daily	73.91

Notes: All prices are from the Ontario Drug Benefit Formulary (accessed Oct 2024), unless otherwise indicated, and do not include dispensing fees. Annual costs based on 365 days per year.[39]

This table has not been copy-edited.

[a]Recommended doses from the appropriate product monographs unless otherwise indicated.

Table 17: Distribution of Second-Line Treatments Based on First-Line Use

Second-line treatment	First-line treatment								
	Glatiramer acetate	Interferon beta-1a	Interferon beta-1b	Teriflunomide	Dimethyl fumarate	Ocrelizumab	Ofatumumab	Natalizumab	Cladribine
Glatiramer acetate	**0% NA**	0%	0%	0%	0%	0%	0%	0%	0%
Interferon beta-1a	0%	**NA 0%**	0%	0%	0%	0%	0%	0%	0%
Interferon beta-1b	0%	0%	**0% NA**	0%	0%	0%	0%	0%	0%
Teriflunomide	0%	0%	0%	**NA 0%**	0%	0%	0%	0%	5%
Dimethyl fumarate	4%	2%	2%	2%	**0 NA %**	0%	0%	0%	10%
Ocrelizumab	30%	30%	30%	30%	30%	**0 NA %**	65%	45%	35%
Ofatumumab	50%	52%	52%	52%	60%	80%	**NA 0%**	50%	45%
Natalizumab	5%	5%	5%	5%	5%	10%	20%	**NA 0%**	5%
Cladribine	10%	10%	10%	10%	5%	5%	5%	0%	**NA 0**
Alemtuzumab	0%	0%	0%	0%	0%	5%	10%	5%	0
Fingolimod	1%	1%	1%	1%	0%	0%	0%	0%	0
Total	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**

Notes: No literature was identified to inform distributions; as such, these are based on clinical expert opinion.

This table has not been copy-edited.

Table 18: Review of Literature of First-Line Treatments for RRMS

Study	Population	Intervention(s)	Comparator(s)	Source of evidence used for the clinical inputs	Conclusions of study	Challenges and limitations
Cost-consequence analysis of ofatumumab for the treatment of relapsing-remitting multiple sclerosis in Canada[66]	RRMS	Ofatumumab	Ocrelizumab, teriflunomide, dimethyl fumarate, glatiramer acetate, interferon beta-1a, 1b, cladribine, natalizumab and fingolimod	ASCLEPIOS trial of ofatumumab compared with teriflunomide for patients with RRMS. Treatment effect for other comparators was derived from an NMA by Samjoo et al.[50]	Ofatumumab vs cladribine: greater costs, greater QALYs Ofatumumab vs natalizumab: lower costs, lower QALYs	ASCLEPIOS trial informing treatment efficacy was not restricted to those with DMT-naive RRMS Model did not consider treatment sequencing; no subsequent treatment was incorporated after discontinuation of first-line treatment Cladribine and natalizumab were included in a scenario analysis only Authors noted that ofatumumab may shift the treatment paradigm toward early high-efficacy treatment for patients with RRMS, however, analyses were not specified to cladribine or natalizumab
Benefits of early highly effective vs. escalation treatment strategies in relapsing multiple sclerosis estimate using a treatment sequence model (Netherlands)[42]	Treatment-naive relapsing MS	Early highly effective treatment: patients start with cladribine, ocrelizumab, ofatumumab or natalizumab in line 1 and can receive other high-efficacy DMTs (cladribine, ocrelizumab, ofatumumab,	Escalation: DMT sequences escalating from less to more efficacious drugs (interferon beta, dimethyl fumarate, teriflunomide, glatiramer acetate, ponesimod, ozanimod and fingolimod)	Efficacy (annualized relapse rates and 24-week confirmed disability progression): NMA Probability of switching due to side effects: discontinuation rates in DMT vs. placebo in respective clinical trials	Ocrelizumab – cladribine – natalizumab – alemtuzumab is the most cost-effective early highly effective treatment sequence	NMA informing treatment efficacy did not consider efficacy based on line position (i.e., efficacy of DMT was assumed to be constant regardless of line of use) Switching probabilities due to AEs were based on naive comparisons Background probabilities were based on a heterogenous sample of patients with MS, and the clinical trials were not, resulting in the findings being

Study	Population	Intervention(s)	Comparator(s)	Source of evidence used for the clinical inputs	Conclusions of study	Challenges and limitations
		natalizumab or alemtuzumab) in lines 2 to 4				most applicable to the average patient with MS for which efficacy of DMTs has been established. Several first-line comparators in the escalation sequence are not relevant in the Canadian context (ponesimod, ozanimod and fingolimod)
NICE review of natalizumab for the treatment of adults with highly active RRMS[67]	RES-RRMS	Natalizumab	Beta interferon, glatiramer acetate and BSC	Natalizumab-post hoc analysis of AFFIRM study Comparators-ITC based on systematic reviews in the general RRMS population	Natalizumab associated with inc. costs and inc. QALYs	Study was not specific to a DMT-naive RRMS population AFFIRM study used to populate natalizumab efficacy is not in an exclusively DMT-naive population;[68] therefore, natalizumab efficacy is not first-line Efficacy data for comparators is from general the RRMS population, not RES-RRMS Model did not consider subsequent lines of therapy or treatment sequencing Relevant comparators to Canadian setting not included (i.e., ocrelizumab and ofatumumab)
CDA-AMC HTA[19]	Patients who are DMT-naive, with highly active relapsing MS	• Alemtuzumab • Cladribine • Fingolimod • Natalizumab	• Glatiramer acetate • Interferon beta-1a • Interferon beta-1b • Teriflunomide • Dimethyl fumarate	Not available: an economic evaluation could not be conducted due to significant clinical data gaps, including the methodological limitations precluding assessment of comparative treatment efficacy in an ITC	The comparative cost-effectiveness of first-line treatments for highly active relapsing MS is unknown.	Population narrower than population of this review (i.e., restricted to highly active only) Unable to estimate cost-effectiveness.

Study	Population	Intervention(s)	Comparator(s)	Source of evidence used for the clinical inputs	Conclusions of study	Challenges and limitations
			• Ocrelizumab • Ofatumumab			

BSC = best supportive care; DMT = disease-modifying therapy; HTA = Health Technology Assessment; ITC = indirect treatment comparison; MS = multiple sclerosis; NMA = network meta-analysis; QALY = quality-adjusted life-year; RES = rapidly evolving severe; RRMS = relapsing-remitting multiple sclerosis

Note: This table has not been copy-edited.

Table 19: Key Characteristics of 6 High-Efficacy Disease-Modifying Therapies Available in Canada

Treatment	Mechanism of action	Indication[a]	Recommended dosage and mode of administration	Serious adverse effects and safety issues and contraindications
Cladribine (Mavenclad)	Selective immunosuppressant	Monotherapy for the treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS) to reduce the frequency of clinical exacerbations and delay the progression of disability.	The recommended cumulative dose is 3.5 mg/kg body weight over 2 years, administered as 1 treatment course of 1.75mg/kg per year, followed by observation for another 2 years. Each treatment course consists of 2 treatment weeks, 1 at the beginning of the first month and 1 at the beginning of the second month of the respective year. Each treatment week consists of 4 or 5 days on which a patient receives 10 mg or 20 mg (1 or 2 tablets) as a single daily dose, depending on body weight.	Lymphopenia, leukopenia, decrease in neutrophil count, infections, cancer
Natalizumab (Tysabri)	Selective adhesion molecule inhibitor	Monotherapy for the treatment of patients with relapsing-remitting form of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations, to decrease the number and volume of active brain lesions identified on MRI scans and to delay the progression of physical disability.	The recommended dose is 300 mg IV infusion every 4 weeks. Do not administer as an IV push or bolus infection. Infuse over approximately 1 hour. Observe patients during the infusion and for 1 hour after the infusion is complete for signs and symptoms of infusion reactions.	Increased risk of progressive multifocal leukoencephalopathy (PML), granule cell neuropathy secondary to opportunistic infection caused by JC virus,

Treatment	Mechanism of action	Indication[a]	Recommended dosage and mode of administration	Serious adverse effects and safety issues and contraindications
Ocrelizumab (Ocrevus)	Selective immunomodulator (anti CD20 monoclonal antibody)	For the treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS) with active disease defined by clinical and imaging features For the management of adult patients with early primary progressive multiple sclerosis as defined by disease duration and level of disability, in conjunction with imaging features characteristic of inflammatory activity	Initial dose: 300mg IV infusion, followed 2 weeks later by a second 300mg IV infusion. Subsequent doses: single 600mg IV infusion every 6 months	Severe cardiovascular events and severe mucocutaneous reactions Infusion reactions, upper respiratory tract infections, nasopharyngitis
Ofatumumab (Kesimpta)	Selective immunomodulator (anti-CD20 monoclonal antibody)	For the treatment of adult patients with relapsing-remitting multiple sclerosis with active disease defined by clinical and imaging features	Initial dosing of 20 mg by subcutaneous injection at weeks 0, 1 and 2, followed by subsequent monthly dosing of 20 mg by subcutaneous infection, starting at week 4.	Progressive multifocal leukoencephalopathy Upper respiratory tract infections Injection-related reactions and injection site reactions
Fingolimod (Gilenya)	Sphingosine 1-phosphate receptor modulator	For the treatment of patients (including pediatric patients 10 to 18 years of age) with RRMS to reduce the frequency of clinical exacerbations and to delay the progression of physical disability. It is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, 1 or more therapies for MS.	0.5 mg/day Oral capsules	PML, skin cancer, infections (varicella; VZV vaccination recommended), heart block. Contraindicated in patients who are hypersensitive to fingolimod, who are at increased risk for opportunistic infection, have hepatic insufficiency, active severe infections, known active malignancies, major cardiovascular issues, severe arrhythmias, and pregnancy.
Alemtuzumab (Lemtrada)	Anti-CD52 monoclonal antibody	For adult patients with RRMS, with active disease defined by clinical and imaging features, who have had an inadequate	Initial treatment cycle: 12 mg/ day for 5 consecutive days by IV infusion. Second treatment cycle: 12 mg/day for 3 consecutive days administered	Autoimmune and immune-mediated conditions, infections, infusion reactions, stroke, malignancies. Contraindicated in patients

Treatment	Mechanism of action	Indication[a]	Recommended dosage and mode of administration	Serious adverse effects and safety issues and contraindications
		response to interferon beta or other DMTs	12 months after the initial treatment course.	who are hypersensitive to alemtuzumab or to any ingredient in the formulation or component of the container; are infected with HIV; have active or latent TB, active severe infections, or active malignancies; are on antineoplastic or immunosuppressive therapies; or have a history of PML.

DMT = disease-modifying treatment; MS = multiple sclerosis, PML = progressive multifocal leukoencephalopathy; RRMS = relapse-remitting multiple sclerosis.

Note: This table has not been copy-edited.

[a]Per Health Canada–approved indications.

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