Reimbursement Review

Review Report

Cladribine & Natalizumab

(Streamlined Drug Review)

Therapeutic area: Relapsing Remitting Multiple Sclerosis

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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 episodes of attacks 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 (DMTs) 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 DMTs with lower-cost and more favorable 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 high-efficacy DMTs as first-line treatment, even with less favorable safety and cost profiles.

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

Natalizumab and cladribine are two 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 last 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 two high efficacy DMTs currently reimbursed as first line treatment of RRMS, ocrelizumab and ofatumumab. However, 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.

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. We used a recently published indirect treatment comparison – network meta-analysis (also called a mixed treatment comparison) – that provided the most up-to-date evidence simultaneously comparing natalizumab and cladribine with other treatments for RRMS. We also considered extensive input provided by clinicians and patients.

What Did We Find?

Clinical Evidence

The network meta-analysis showed that natalizumab and cladribine are more effective than all but one of the lower efficacy DMTs of interest in reducing the frequency of relapses over two years of treatment. There was no difference between treatment with natalizumab and with cladribine with other select treatment comparators including two high efficacy DMTs with respect to the number of people experiencing serious adverse events or discontinuing 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. When compared to peginterferon beta-1a, natalizumab resulted in 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
CI	confidence interval
CNS	central nervous system
DMT	disease modifying treatment
HRQoL	health related quality of life
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

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; 60% of adults diagnosed with MS are between the ages of 20 and 49 years old.[3] In Canada, the average age of MS diagnosis is 43.[3] Women are three times more likely to be diagnosed with MS than men; 75% of people in Canada living with MS are women.[3]

The disease attacks myelin, the protective covering of the of nerve fibers. The demyelination of central nerve fibers 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 with 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. In the majority of cases, MS is characterized by reversible episodes of neurological dysfunction, 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, difficulty speaking and swallowing.

Diagnosis of MS relies on clinical, imaging, and laboratory findings. The long-standing McDonald criteria are used for diagnosing MS, and the 2017 revision of the McDonald criteria have facilitated 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 diagnosis.[5] The 2017 McDonald criteria enable more patients with a first attack 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 (CIS), relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS).[7] Most people who develop MS are initially diagnosed with RRMS, characterized by discrete episodes of neurological impairment or attacks of symptoms (called relapses) which 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. Relapse rate and degree of recovery after relapses predict long-term disability.[8] In Canada about 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; and more recently, “highly active” MS and is commonly identified based on relapse frequency, relapse severity, relapse recovery, and key lesions on brain scans.[5] However, the term has been used relatively recently 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 therapies (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 slowing the disease progression in some patients, but they do not reverse damage that has already occured.[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 representing 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, route of administration (oral vs. injectable), and availability may influence treatment selection.

There are two treatment approaches for patients 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 escalating to more effective or potent therapies based on continued disease activity and inadequate symptoms control. The second approach is the "early highly-efficacy treatment" or "early intensive treatment" approach which involves starting therapy with a high-efficacy drug first-line with a greater likelihood of controlling disease activity and symptoms control but also a higher potential for serious adverse events, although the actual frequency of these serious adverse events 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, and evidence that many newer, higher-efficacy drugs may have worse cost-effectiveness compared with low 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 with high disease activity.[15-18] The Canadian MS Working Group now considers high-efficacy DMTs as starting treatment options for patients with high disease activity, aggressive disease presentation, or rapidly evolving symptoms at onset, as these patients are at significant risk of early disability worsening.[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 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. The clinical experts highlighted that earlier use of high-efficacy DMTs for patients with RRMS particularly those with high disease activity, or rapidly evolving MS at onset could prevent irreversible damage to the nervous system that may result from 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 Canadian MS Working Group: fingolimod, cladribine, natalizumab, alemtuzumab, ofatumumab, and ocrelizumab.[5] Only two: ofatumumab and ocrelizumab, 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 in RRMS there is a shift in treatment paradigm from the traditional escalation treatment approach to early high-efficacy treatment approach. Currently, two high-efficacy DMTs: ofatumumab (SC injection) and ocrelizumab (IV infusion) are reimbursed. 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 RRMS patient population, 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 that 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 where 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 an 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, as 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 when compared to 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, and two highly active DMTs ocrelizumab and ofatumumab).

The HTA was published in May 2024 and included a systematic review of published 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 examination of individuals with highly active disease a priori was not a consideration at the time of most of the original trials, as the science had not evolved sufficiently to identify this as a relevant subgroup that should be captured for specific/differential examination.

As CDA-AMC HTA reviews are not accompanied by reimbursement recommendations and proposed reimbursement criteria for public drug plan implementation, 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 through the new CDA-AMC committee, FMEC (Formulary Management Expert Committee). For this review the drug plans identified natalizumab and cladribine as the drugs of interest. These two drugs were thought to meet a particular unmet need for first line therapy in select patients, that is not met by the two high efficacy drugs (i.e., ofatumumab and ocrelizumab) currently reimbursed in first line. Considering the limited evidence identified with regards to comparative efficacy and safety of DMTs in the highly active RRMS population, 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 terminology with no established and universally accepted definition, which partly explains the lack of clinical trials to date recruiting specifically these patients, although some conducted post hoc analyses on this subgroup with varying definitions. The decision for this revision also considered input provided by external partners on 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 IgG4 κ monoclonal antibody selective for α4-integrin on the surface of lymphocytes, that is essential in the process by which lymphocytes gain access to the brain. Natalizumab blocks alpha-4 integrin and prevents lymphocytes from entering the CNS, and attack myelin.[20]

Natalizumab is the first in a class of agents 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 available information, the clinical benefits of natalizumab continue to outweigh the potential risks, and marketing of the drug for severe RRMS resumed.[21,22]

Natalizumab received notice of compliance (NoC) 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, 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 multiple sclerosis.[23] Natalizumab is administered by intravenous infusion, at a recommended dose of 300 mg every four 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 meet all of the following criteria: (1) failure to respond to full and adequate courses of treatment with at least two DMTs or have contraindications to or be intolerant of these therapies; (2) significant increase in T2 lesion load compared to a previous MRI or at least one gadolinium-enhancing lesion; and (3) two or more disabling relapses in the previous year.[25]

The data protection for natalizumab ended on Sep 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 UK.[28]

Cladribine

Cladribine (Brand name Mavenclad) is a synthetic chlorinated deoxyadenosine analog 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 NoC 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, one or more therapies for RRMS. Cladribine is available as an orally administered tablet, and the Health Canada-approved dose 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] 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 are met: (1) for use in patients who have had an inadequate response to, or are unable to tolerate, one previous therapy for RRMS, and who have had at least one relapse within the previous 12 months; (2) the patient is under the care of a specialist who has experience in the diagnosis and management of RRMS and; (3) there is a price reduction. CDEC aligned their recommendations with the Health Canada indication for cladribine which states that it is generally recommended for RRMS patients who have had an inadequate response to, or are unable to tolerate, one or more therapies for RRMS; however, most patients enrolled in CLARITY were treatment naive. Health Canada expressed concern about the higher proportions of patients treated with cladribine in CLARITY who experienced certain notable adverse events, such as lymphopenia, herpes zoster infection, and neoplasms, as 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.

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 vs 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. Of note, input was provided on the original review scope that included patients with highly active RRMS, before the scope was expanded to the broader RRMS patient population.

Patient Group

MS Canada provided input on this review. The input noted 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 and 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 with public drug plans continuing 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 soon as possible to avoid neurological damage and irreversible disability caused by suboptimal management of disease activity. They cited American 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 as well as place the patient at the center of their disease management.

MS Canada noted the lack of head-to-head comparison studies is a longstanding challenge in the pharmacoeconomic review of multiple sclerosis (MS) disease-modifying therapies for public payer decision-making. There are no MS DMTs formally indicated as first-line treatments for individuals with "highly active relapsing MS", as such MS Canada did not believe that it is 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) which is 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. As the previous input on the HTA remained relevant to the current review, it was resubmitted to us in addition to new input on the current review scope.

The 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 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. They 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. The 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 globally accepted standards for disease management in MS.

In the input on the HTA, CNMSC's expressed concern with CADTH's search terms, and the expectation of identifying clinical trials focused solely on the "aggressive/highly active" MS population. They highlighted that using the search terms "aggressive/highly active MS" is unlikely to reveal the full evidence base to address the key question for that review noting that this terminology is relatively recent and, as a result, it has not traditionally been used as a "selection criterion" to design specific trials in this population. Historically, there were many patients with highly active MS enrolled in clinical trials, given the very limited treatment options available at the time of pivotal trials and that 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, they indicated that the original phase 3 RCTs for natalizumab (and the other DMTs) should have been within scope for the HTA, as 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 and furthermore excluding these studies would disadvantage drugs such as natalizumab that were studied at a time when few other therapies were available.

In the input for the current review, CNMSC reiterated the issues regarding limited clinical trial data for natalizumab and cladribine compared to other DMTs in patients with highly active RRMS and the need for including real world evidence (RWE) 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 to 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, given the clinical/disability and economic implications of delayed therapy and further, raised the issue of equitable access noting that some provinces already fund these drugs on a case-by-case basis; Quebec also 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 non-comparative, 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 being 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 to other DMTs used in first line for treating people with RRMS.
- To summarize feedback from patients, clinicians, and manufacturer perspectives on the needs for first -line therapies for RRMS.
- To compare costs for natalizumab and cladribine to 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 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 CDA-AMC's *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 multi-file search. Search concepts were developed based on the elements of the PICOS framework and research questions. The main search concepts were RRMS and natalizumab or cladribine. CDA-AMC-developed search filters 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. See Appendix 1 for the detailed search strategies. The initial search was completed on September 20, 2024. Regular alerts updated 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 population, intervention, comparator, and study design criteria were selected for inclusion. In the first level of screening, titles and abstracts were reviewed and 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 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 one 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 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 forms the evidence base for this streamlined drug review.

Table 1: Study Selection Criteria

Criteria	Description
Population	Patients with RRMS who are DMT-naïve
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
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 AEs: injection-related reactions, opportunistic infections, serious infections, PML, lymphopenia, neutropenia, malignancies
Study design	Systematic reviews of RCTs with network meta-analysis
Search dates	Up to September 20, 2024 (no date limits)

9-HPT = 9-Hole Peg Test; AE = adverse event; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; HRQoL = health-related quality of life; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; MSNQ = Multiple Sclerosis Neuropsychological Questionnaire; MSQLI = Multiple Sclerosis Quality of Life Inventory; MS-QLQ27 = 27-item Multiple Sclerosis Quality of Life Questionnaire; MSWOL-54 = Multiple Sclerosis Quality of Life-54; PASAT 3 = 3-second Paced Auditory Serial Addition Task; PML = progressive multifocal leukoencephalopathy; RCT = randomized controlled trial; RRMS = relapsing remitting multiple sclerosis; SDMT = Symbol Digit Modality Test; T25-FW = Timed 25-Foot Walk.
[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 the treatment of people with RRMS. The authors 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 agent or placebo as a control arm; non nonpharmacological treatments, and over-the counter drugs were not considered. The review included RCTs that evaluated one or more of the following pharmacological interventions as monotherapy, compared to placebo or to another active agent: The treatments compared were: 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 1-a and beta 1-b, leflunomide, methotrexate, minocycline, mycophenolate mofetil, ofatumumab, ozanimod, ponesimod, rituximab, siponimod and steroids.

Outcome measures

The authors estimated the relative effects of the competing interventions according to the following primary efficacy and safety outcomes:

(1) Relapses (over 12, 24, or 36 months), defined as newly developed or recently worsened symptoms of neurologic dysfunction that last 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.

(2) Disability worsening (over 24 or 36 months), defined as at least a 1-point Expanded Disability Status Scale (EDSS) increase or a 0.5-point increase if the baseline EDSS was greater than or equal to 5.5, confirmed during two subsequent neurological examinations separated by at least a six-month interval free of attacks. Disability worsening confirmed after only three 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 (where 0 is normal, 3 mild disability, 6 care requirement, 7 wheelchair use, and 10 is death from MS).

(3) discontinuation due to AEs

(4) Serious adverse events (SAEs): number of participants with any (one or more) SAEs, defined according to the authors of the 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 authors assessed the risk of bias of each included study 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. The authors judged the risk of bias of each study on each criterion and classified it as being at 'low', 'high', or 'unclear' risk of bias. The authors performed sensitivity analyses including only 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 (MD) or standardised mean differences (SMD) were reported for continuous outcomes. The results of the network meta-analysis were presented as summary relative effect sizes (RR, MD, or SMD) for each possible pair of treatments.

The authors performed network meta-analysis using a random-effects model within a frequentist setting assuming equal heterogeneity across all comparisons and accounted for correlations in multi-arm studies. They assessed 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 GRADE approach. Since 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 contextualised approach which incorporates the value of individual outcomes in the overall interpretation of the results which 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 and the certainty of evidence for each outcome was graded considering study limitations, indirectness, inconsistency, imprecision of effect estimates, and risk of reporting bias assigning four 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 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 1-a and beta 1-b, leflunomide, methotrexate, minocycline, mycophenolate mofetil, ofatumumab, ocrelizumab, ozanimod, ponesimod, rituximab, siponimod, steroids
Outcome measures	**Primary outcomes** • Relapse (proportion of participants who experienced new relapses over 12, 24, or 36 months after randomisation or at the end of the study. • Disability worsening (proportion of participants who experienced disability worsening over 24 or 36 months after randomisation or at the end of the study) • Discontinuation due to AEs • SAEs **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)

Characteristic	Description
	• 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 therapies; 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 and 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 were included in analyses.

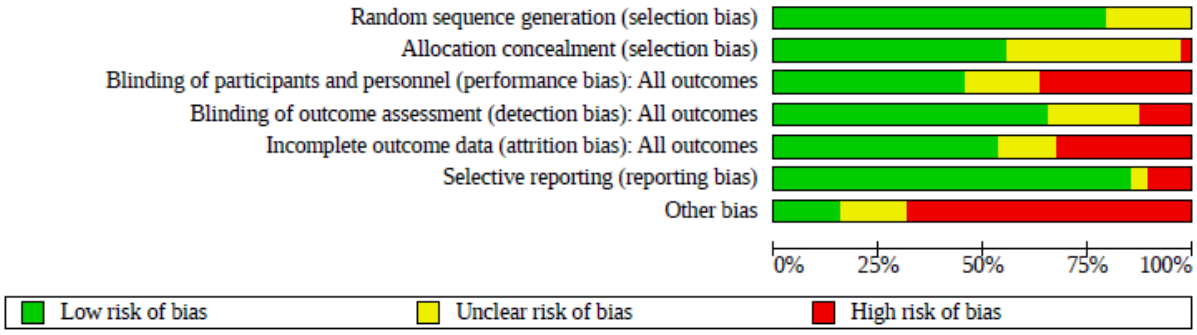
Of the 50 included studies, 1 included only people with MS previously treated with DMTs; 5 included only people with MS previously untreated with DMTs, 17 did not report data about previous treatments with DMTs, and 27 included a mixed population of patients with and without previous treatment with DMTs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

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

Risk of bias in included studies

The risk of bias assessments with review authors' judgement about each risk of bias item presented as percentages across all included studies is summarized in Figure 1.With regards to the six 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 as being at high risk of bias for selective outcome reporting due to lack of reporting of all prespecified outcomes. Thirty-four studies (68%; this included the Affirm trial for natalizumab and the CLARITY trial for cladribine) were judged as being 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 graph: review authors' judgement about each risk of bias item across all included studies



Results of the network meta-analysis

The authors reported treatment estimates from pairwise meta-analyses (direct comparisons, mostly with placebo) and network meta-analyses estimates combining direct and indirect comparisons of treatment against placebo and against each other treatment included in the network. The findings of the network meta-analyses are summarized below.

Primary outcomes

I. Relapses

Relapses over 12 months: data were reported in 18 studies involving 9310 participants with RRMS (25.49% of the participants in the review) and assessing 13 treatments. Nine treatments assessed in 18 studies were compared to placebo, of which 7 treatments were evaluated in head-to-head comparisons in 7 studies.

Using placebo as a common comparator, treatment with natalizumab results in a large reduction of people with 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 larger decrease in the number of people with relapses over 12 months compared with interferon beta-1a and 1b and interferon beta 1a. There was no difference with respect to other treatments.

There was insufficient data to evaluate cladribine compared to 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 to placebo, 10 treatments were evaluated in head-to-head comparisons in 11 studies and 2 studies involving 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), and natalizumab (RR 0.56, 95% CI 0.48 to 0.65; high-certainty evidence) resulted in a large decrease in the number of people with relapses.

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

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

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

Relapses over 36 months 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

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

CI = confidence interval; NA = not available; RR = risk ratio
[1] Only data for the treatments of interest to this review were extracted from the network meta-analysis netleague tables.
Source: Reprinted with permission (CC BY-NC) from Gonzalez-Lorenzo (2024), Table 2 and Table 3.[31]

II. Disability worsening

Disability worsening over 24 months: data were reported in 31 studies and 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 to 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 of the number of people with disability worsening (RR: 0.59, 95% CI: 0.46 to 0.75; moderate-certainty evidence).

Treatment with cladribine may result in a small reduction of 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 larger decrease in the number of people with disability worsening over 24 months compared only with interferon beta-1a. There was no difference between treatment with natalizumab and other select treatment comparators with respect to the number of people with disability worsening over 24 months.

There was no difference between treatment with cladribine and other select treatment comparators with respect to the number of people with 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

Comparators[1]	Natalizumab	Cladribine
	RR (95% CI)	
glatiramer acetate	0.80 (0.59,1.09)	1.03 (0.76,1.41)
interferon beta-1a and 1b	0.19 (0.02,1.96)	4.45 (0.42,47.01)
Interferon beta-1a	**0.64 (0.46,0.90)**	1.29 (0.92,1.80)
Interferon beta-1b	0.77 (0.56,1.07)	1.07 (0.78,1.47)
teriflunomide	0.77 (0.56,1.07)	1.07 (0.77,1.48)
dimethyl fumarate	0.91 (0.67,1.22)	0.91 (0.68,1.23)
ocrelizumab	0.98 (0.61,1.55)	0.85 (0.53,1.34)
ofatumumab	1.09 (0.71,1.68)	0.76 (0.49,1.16)

CI = confidence interval; RR = risk ratio
[1] Only data for the treatments of interest to this review were extracted from the network meta-analysis netleague tables.
Source: Reprinted with permission (CC BY-NC) from Gonzalez-Lorenzo (2024), Table 5.[31]

III. Treatment discontinuation due to AEs

Data for treatment discontinuation due to AEs were available from 43 studies and 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 to 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). 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 and with cladribine and other select treatment comparators with respect to the number of people discontinuing treatment due to AEs.

Table 5: Treatment Discontinuation Due to AEs

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

CI = confidence interval; RR = risk ratio
[1] Only data for the treatments of interest to this review were extracted from the network meta-analysis netleague tables.
Source: Reprinted with permission (CC BY-NC) from Gonzalez-Lorenzo (2024), Table 7.[31]

IV. SAEs

Data for SAEs were available from 35 studies and 33,998 participants with RRMS (93% of those included in the review) and assessing 17 treatments. Eleven treatments, assessed in 18 studies, were compared to placebo, 14 treatments were evaluated in head-to-head comparisons in 21 studies, and two studies involving 2,751 participants had both placebo and active treatment arms.

Compared to placebo treatment with natalizumab may result in a trivial increase in people who experience SAEs (OR: 1.24, 95% CI: 0.73 to 2.09; low-certainty evidence). Treatment 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 and with cladribine and other select treatment comparators with respect to the number of people experiencing SAEs.

Table 6: SAEs

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

CI = confidence interval; RR = risk ratio
[1] Only data for the treatments of interest to this review were extracted from the network meta-analysis netleague tables.
Source: Reprinted with permission (CC BY-NC) from Gonzalez-Lorenzo (2024), Table 8.[31]

Secondary outcomes

I. 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 to placebo.

Using placebo as a common comparator, treatment with natalizumab results in a large reduction of 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 to placebo, 7 treatments were evaluated in head-to-head comparisons in 9 studies and one 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

Comparators[1]	Natalizumab	Cladribine
	RR (95% CI)	
glatiramer acetate	**0.18 (0.10,0.33)**	NA
Interferon beta-1a	**0.32 (0.16,0.62)**	NA
Interferon beta-1b	0.68 (0.30,1.56)	NA
teriflunomide	NA	NA
dimethyl fumarate	**0.22 (0.12,0.38)**	NA
ocrelizumab	0.86 (0.42,1.76)	NA
ofatumumab	NA	NA

CI = confidence interval; RR = risk ratio
[1] Only data for the treatments of interest to this review were extracted from the network meta-analysis netleague tables.
Source: Reprinted with permission (CC BY-NC) from Gonzalez-Lorenzo (2024), Appendix 7.[31]

II. New or enlarging T2-weighted MRI lesions

New or enlarging T-2 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, a large increase in new or enlarging T2-weighted MRI lesions may have resulted in people treated with natalizumab (RR: 2.01, 95% CI: 0.43 to 9.51).

The network estimates of new or enlarging T-2 weighted MRI lesions at 12 months are summarized in Table 8 for select treatments of interest:

There is no difference between natalizumab and glatiramer acetate, interferon beta 1a and interferon beta 1b in reducing new or enlarging T-2 weighted MRI lesions. No data were available with respect to other select treatments. There were insufficient data comparing cladribine to other treatments for this outcome.

New or enlarging T-2 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 ten treatments. Two treatments, assessed in 2 studies, were compared to placebo.

Using placebo as a common comparator, treatment with natalizumab resulted in a large reduction of 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

Comparators[1]	Natalizumab	Cladribine
	RR (95% CI)	
glatiramer acetate	0.85 (0.72,1.01)	NA
Interferon beta 1a	3.98 (0.86,18.45)	NA
Interferon beta-1b	0.95 (0.89,1.02)	NA
teriflunomide	NA	NA
dimethyl fumarate	NA	NA
ocrelizumab	NA	NA
ofatumumab	NA	NA

CI = confidence interval; RR = risk ratio
[1] Only data for the treatments of interest to this review were extracted from the network meta-analysis netleague tables.
Source: Reprinted with permission (CC BY-NC) from Gonzalez-Lorenzo (2024), Appendix 8.[31]

III. 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 to 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 compared to treatment with glatiramer acetate, and interferon beta 1a. There is no data comparing natalizumab to other selected treatments.

There were insufficient data comparing cladribine to other treatments for this outcome.

Table 9: Cognitive Decline

Comparators[1]	Natalizumab	Cladribine
	RR (95% CI)	
glatiramer acetate	**-1.19 (-2.25, -0.13)**	NA
Interferon beta-1a	**-1.09 (-2.13, -0.04)**	NA
Interferon beta-1b	-0.18 (-1.09,0.72)	NA

teriflunomide	NA	NA
dimethyl fumarate	NA	NA
ocrelizumab	NA	NA
ofatumumab	NA	NA

CI = confidence interval; NA = not available, RR = risk ratio.
[1] Only data for the treatments of interest to this review were extracted from the network meta-analysis netleague tables.
Source: Reprinted with permission (CC BY-NC) from Gonzalez-Lorenzo (2024), Appendix 10.[31]

IV. 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 in comparison to placebo from the pivotal trials of natalizumab and cladribine.

V. 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 to 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 arms.

Using placebo as a common comparator a trivial increase in the number of deaths probably occurred in the people treated with cladribine (OR: 0.98, 95% CI: 0.18 to 5.39). A trivial increase in the number of deaths may have occurred in the 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 b, 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 b, teriflunomide, dimethyl fumarate, ocrelizumab and ofatumumab in MS-related mortality rate.

Table 10: MS-related Mortality

Comparators[1]	Natalizumab	Cladribine
	RR (95% CI)	
glatiramer acetate	5.12 (0.17,156.95)	0.50 (0.05, 5.09)
Interferon beta 1a	4.00 (0.15,106.34)	0.64 (0.08, 5.25)
Interferon beta-1b	6.85 (0.11, 414.99)	0.37 (0.01, 9.58)

teriflunomide	0.59 (0.01, 26.33)	1.52 (0.09, 25.92)
dimethyl fumarate	3.37 (0.09,124.42)	0.76 (0.06,10.10)
ocrelizumab	0.16 (0.00, 7.68)	0.40 (0.02, 7.82)
ofatumumab	0.19 (0.00, 27.85)	0.50 (0.01, 35.96)

CI = confidence interval; RR = risk ratio
[1] Only data for the treatments of interest to this review were extracted from the network meta-analysis netleague tables.
Source: Reprinted with permission (CC BY-NC) from Gonzalez-Lorenzo (2024), Appendix 13.[31]

Critical Appraisal of the Evidence

The authors of the systematic review used validated methods to assess risk of bias in individual studies, using the Cochrane RoB tool. Risk of bias was appropriately assessed independently by two review authors, 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. While this approach is methodologically sound, the review noted 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 impacting the validity of results.

Assumptions for network meta-analyses were tested and discussed. The authors 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, the review acknowledged differences in patient or trial characteristics, especially with newer versus older trials, and potential hidden or unmeasured confounders that might influence treatment effects. The authors stated that no important differences across selected patient characteristics (such as age, disease duration, and baseline EDSS scores) were identified. Details about how patient and trial characteristics were examined and how it was determined that no important differences existed were not described.

Assessment of statistical heterogeneity for all direct pairwise comparisons and for the entire network as also performed. Additionally, an assessment of statistical consistency evaluating the agreement between direct and indirect estimates using two different approaches and used the design-by-treatment model to evaluate the assumption of consistency in the entire network.

The authors 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.

The review noted 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 the authors concluded that the key assumptions of transitivity, heterogeneity and consistency were reasonably met, there was suggestion that some factors were present that may not have been accounted for in the analysis. Moreover, there was limited information provided about how decisions regarding the importance of these influences on results and differences between analyses was made.

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 one non-critical 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, six DMTs available in Canada are considered high efficacy treatments by the Canadian MS Working Group: fingolimod, cladribine, natalizumab, alemtuzumab, ofatumumab, and ocrelizumab.[38] As fingolimod and alemtuzumab are indicated for second-line use only, cladribine, natalizumab, ofatumumab and ocrelizumab are referred to as "high efficacy" treatment in the first line, and the remaining comparators (i.e., glatiramer acetage, 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 to ocrelizumab and teriflunomide, respectively. When compared to 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 to ocrelizumab and teriflunomide, respectively. When compared to 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.

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 two 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	Pre-filled syringe	27.8587	20 mg daily	27.86	10,168

Treatment	Strength	Form	Price ($)	Recommended dosage[a]	Daily cost ($)	Annual cost ($)
Interferon beta-1a (Avonex)	30 mcg/0.5 mL	Pre-filled 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	Pre-filled 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	Pre-filled syringe/pen	1,879.4900[b]	SC injection every two 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	Pre-filled syringe Sensoready pen	2,318.7400[b]	20 mg at weeks 0, 1, 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
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

mcg = microgram; mg = milligram; mL = millilitre; SC = subcutaneously

Note: All prices are from the Ontario Drug Benefit Formulary (accessed Oct 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 Oct 2024).[40]

[c] The total does per patient annually is divided as two treatment courses, one 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 to 20 mg as a single daily dose. For example, a patient weighing 70 kg would take seven 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 two separate IV infusions: a 300 mg infusion, followed two weeks later by a second 300 mg infusion. Subsequent doses are administered as single 600 mg IV infusions every six 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. Clinical experts indicated that the primary reasons for patients to switch from a first-line to a second-line treatment include tolerability concerns, adverse events 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 leading to 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 naïve 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 estimated 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 16). 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 16) , by each second-line treatment's annual cost (Table 11 and Appendix 5, Table 15).

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. Secondly, 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

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

Note: While 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 (**Error! Reference source not found.**)

[a] Estimated by multiplying the expected distribution of patients across second-line treatments by their first line treatment 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 17).

As noted in the challenges and limitations section of the table, none of the literature identified accurately represented the decision problem of this review. More specifically, the identified literature either did not represent the target population for this review (i.e., DMT naïve RRMS), did not include all relevant Canadian comparators, or did not consider subsequent lines of therapy in their analysis. As 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 to first line.

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

As noted in the CDA-AMC 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, as well as the cost-effectiveness of moving natalizumab and cladribine from second-line to first-line in highly active RRMS, is unknown. 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 one of the lower efficacy DMTs of interest in reducing the frequency of relapses over two years of treatment. There was no data to determine comparative efficacy of natalizumab and cladribine compared to two high efficacy DMTs (ocrelizumab and ofatumumab) for preventing relapses over two years.
- Currently 2 generic cladribine submissions are under review with Health Canada.[43] Should any or all 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 estimated in this review.
- Natalizumab was reviewed by CDA-AMC in 2009 and received a reimburse with clinical conditions recommendation.[25] Reimbursement was exclusive to patients having trialed at least 2 DMTs, having 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 CDA-AMC in 2017 and received a reimburse with clinical conditions recommendation.[30] Reimbursement was exclusive to patients who have trialed 1 previous therapy for RRMS and who have had at least 1 relapse in the last 12 months. Reimbursement was conditional on a price reduction.
- No Canadian cost-effectiveness studies were identified based on a literature conducted on November 28, 2024. Relevant grey and published literature has been summarized in Table 17.

Discussion

Summary of the Input & 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 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 understanding of the disease pathophysiology and the optimal management of RRMS have substantially evolved, the inputs asserted that current drug reimbursement policy in Canada has not followed and rarely allows people living with MS to initiate treatment with a high-efficacy therapy requiring 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 evidence highlighted in the systematic review, it appears that for preventing clinical relapses in the short term (generally 24 months or less), natalizumab, and cladribine may be more effective and with similar harms compared to other DMTs used in first-line treatment of RRMS except ocrelizumab and ofatumumab, based on high certainty of evidence. 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. With respect to safety, the number of people who experienced SAEs or discontinued treatment due to AEs were 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 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]

The Health Canada regulatory approval for natalizumab and cladribine that placed them for second- or later-line use for the treatment of patients with RRMS was based on the benefit-risk ratio determined from the observations in the pivotal trials of the two drugs. DMTs for RRMS are associated with specific harms related to their mechanism of action. For cladribine, Health Canada expressed concern about the higher proportions of patients treated with cladribine in the CLARITY trial who experienced certain notable AEs, such as lymphopenia, herpes zoster infection, and neoplasms, as 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 that the benefit-risk profile is favourable as monotherapy for the treatment of RRMS, but states that it is generally recommended in MS patients 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 progressive 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 two 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 two 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. It is also important to note that 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 adverse events 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, such that – in the experts' opinions – for patients who are thought to benefit from either drug, and have no contraindications, the only barrier to using these treatments is reimbursement restrictions, rather than 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). It may therefore 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 like inflammatory bowel disease (IBD) that may be exacerbated by B-cell direct 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 and 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 also be more suitable for patients who are planning to become pregnant because the maximum recommended treatment duration is two 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 intravenous infusions and 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 were DMT-naïve 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 to a strictly DMT-treatment naïve population may be limited. Second, most of the included treatments were evaluated in few trials; data for both natalizumab and cladribine came from only one RCT each. Third, the efficacy of all the treatments beyond two years is uncertain, with only four of the 50 included studies contributing to 36 months of treatment duration. This is particularly important with a chronic neurologic disease like 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. Fifth and lastly, there was insufficient data for some outcomes including health-related quality of life and symptoms in the trials 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 as compared with escalating from lower efficacy drugs. However, there are currently only two high efficacy DMTs that are publicly reimbursed for upfront treatment of RRMS, both with 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 for preventing relapses at 2 years both natalizumab and cladribine are more effective than almost all currently reimbursed low efficacy drugs that are required to be trialed initially. Importantly, neither natalizumab nor cladribine were less favourable with respect to commonly reported serious adverse events than all treatment comparators, including both lower-efficacy and high-efficacy first-line treatments.

This streamlined drug review that integrates extensive input from patient groups and clinicians with best available evidence, 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 first line. 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, while there were studies included in the NMA that included patients who were DMT naïve, the NMA evidence is from a mixed population of those who were DMT naïve and DMT experienced. As the evidence was from a mixed population, no literature in an exclusively DMT naïve population was available to estimate the comparative effectiveness of cladribine and natalizumab in first line, compared with other treatments available in first line. However, given the totality of 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. Relative to these therapies, cladribine and natalizumab have higher annual treatment costs using public list prices. Looking at the full treatment pathway, should the patient require 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 then they would likely be considered cost effective relative to these therapies. Relative to low efficacy DMTs, their cost effectiveness is uncertain in the absence of evidence.

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Appendix 1: Literature Search Strategy

Clinical Literature Search

Overview

Interface: Ovid
Databases

- MEDLINE All (1946-present)
- Embase (1974-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 one 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
.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, we may have included antiquated, noninclusive, or potentially stigmatizing terms that may have appeared in past and present literature. We recognize and acknowledge 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.

Multi-Database 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

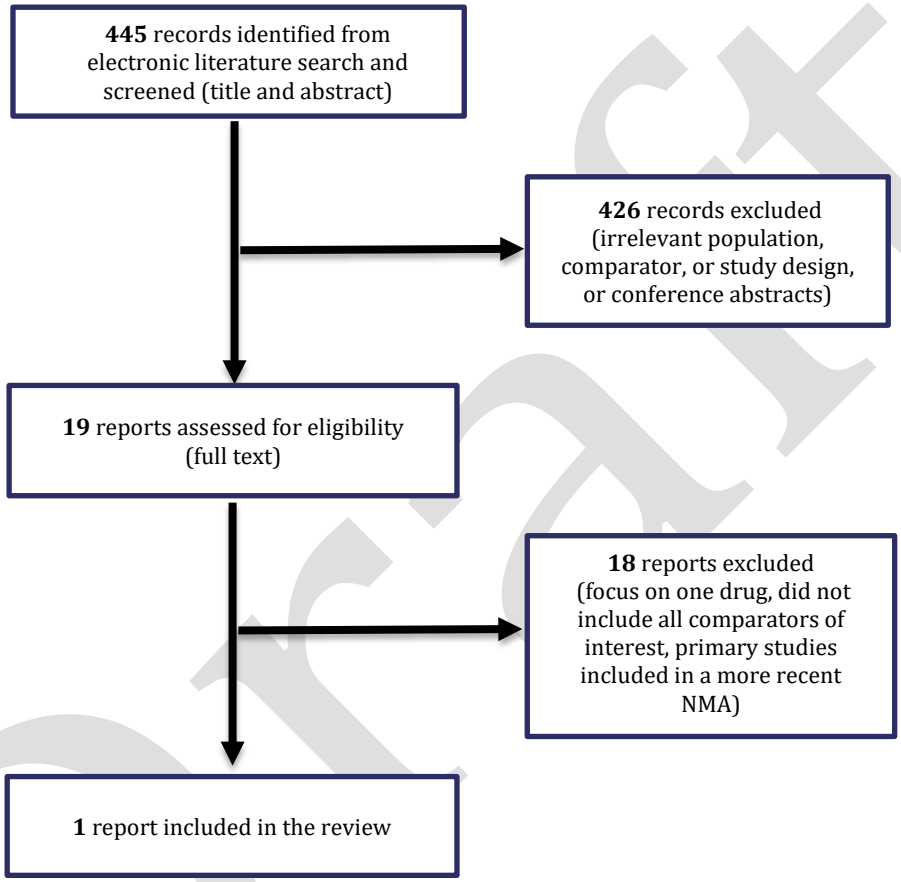
Grey Literature

Search dates: September 20-23, 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

Figure 2: PRISMA Flowchart of Selected Reports



Appendix 3: List of Excluded Studies

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 µg intramuscular; interferon beta-1a 44 µg 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 one outcome (no evidence of disease activity NEDA)
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)	β-interferon, glatiramer acetate, mitoxantrone, natalizumab, fingolimod,	None	Focus on cognition

		teriflunomide, dimethyl fumarate, alemtuzumab, cyclophosphamide, laquinimod, daclizumab, ocrelizumab, cladribine, azathioprine, rituximab, and ozanimod		
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-interferon beta-1a (Plegridy), teriflunomide	Academic	More recent NMA available
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, intravenous immunoglobulins, and long-term corticosteroids	Academic (Cochrane)	More recent NMA available

Appendix 4: Critical Appraisal of the Included Study

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomized or non-randomized studies of healthcare interventions, or both

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) ☐ Timeframe for follow-up	**Yes** No
2. Did the report of the review contain an explicit statement that the review methods were established prior to 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 key word 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 two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include ☐ OR two reviewers selected a sample of eligible studies and achieved good		**Yes** No

agreement (at least 80 percent), 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 two reviewers achieved consensus on which data to extract from included studies ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), 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 ☐ timeframe 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
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
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 15: 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

mcg = microgram; mg = milligram; mL = millilitre.

Note: 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]

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

Table 16: Distribution of second-line treatment based on first-line use

		First-line treatments								
		Glatiramer acetate	Interferon beta-1a	Interferon beta-1b	Teriflunomide	Dimethyl fumarate	Ocrelizumab	Ofatumumab	Natalizumab	Cladribine
Second-line treatments	Glatiramer acetate	N/A	0%	0%	0%	0%	0%	0%	0%	0%
	Interferon beta-1a	0%	N/A	0%	0%	0%	0%	0%	0%	0%
	Interferon beta-1b	0%	0%	N/A	0%	0%	0%	0%	0%	0%
	Teriflunomide	0%	0%	0%	N/A	0%	0%	0%	0%	5%
	Dimethyl fumarate	4%	2%	2%	2%	N/A	0%	0%	0%	10%
	Ocrelizumab	30%	30%	30%	30%	30%	N/A	65%	45%	35%
	Ofatumumab	50%	52%	52%	52%	60%	80%	N/A	50%	45%
	Natalizumab	5%	5%	5%	5%	5%	10%	20%	N/A	5%
	Cladribine	10%	10%	10%	10%	5%	5%	5%	0%	N/A
	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%**

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

Table 17: 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/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 naïve 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 versus escalation treatment strategies in relapsing multiple sclerosis estimate using a treatments equence model (Netherlands)[42]	Treatment-naïve 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, natalizumab or alemtuzumab) in lines 2-4	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 naïve comparisons Background probabilities were based on a heterogenous sample of MS patients, and the clinical trials were not, resulting in the findings being most applicable to the average MS patient 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 naïve RRMS population AFFIRM study used to populate natalizumab efficacy is not in an exclusively DMT naïve 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 • ocrelizumab • ofatumumab	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.

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

Table 18: 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/ 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 3.5mg/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, one at the beginning of the first month and one 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 10mg or 20mg (one or two 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 magnetic resonance imaging (MRI) scans and to delay the progression of physical disability.	The recommended dose is 300mg 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,
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 (PPMS) as defined by disease duration and level of disability, in	Initial dose: 300mg intravenous infusion, followed 2 weeks later by a second 300mg intravenous infusion. Subsequent doses: single 600mg intravenous infusion every 6 months	Severe cardiovascular events and severe mucocutaneous reactions Infusion reactions, upper respiratory tract infections, nasopharyngitis

		conjunction with imaging features characteristic of inflammatory activity		
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 20mg by subcutaneous injection at weeks 0, 1 and 2, followed by ssubsequent monthly dosing of 20mg 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, one 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 response to interferon beta or other DMTs	Initial treatment cycle: 12 mg/ day for 5 consecutive days by intravenous infusion. Second treatment cycle: 12 mg/day for 3 consecutive days administered 12 months after the initial treatment course.	Autoimmune and immune-mediated conditions, infections, infusion reactions, stroke, malignancies. Contraindicated in patients 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; IV = intravenous; MRI = magnetic resonance imaging; MS = multiple sclerosis, PML = progressive multifocal leukoencephalopathy; RRMS = relapse-remitting multiple sclerosis.
[a] Per Health Canada approved indications.