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

Proposed Project Scope

Cladribine and Natalizumab for Highly Active Relapsing-Remitting Multiple Sclerosis

Date: August 2024

For Stakeholder Feedback

Introduction and Rationale

Multiple sclerosis (MS) is a chronic autoimmune disease with the following clinical manifestations: demyelination, inflammation, neuronal loss and gliosis (scarring).[1] It has been estimated that multiple sclerosis affects 2.3 million people worldwide. Diagnosis is established most common among individuals between the age of 20 and 50 years and females.[1] Environmental risk factors such as Epsteine-Barr virus infection, low vitamin D, obesity and cigarette smoking have been reported to contribute to multiple sclerosis.[2].

Relapsing-remitting multiple sclerosis (RRMS) is the most common type of the disease, representing approximately 85% of all multiple sclerosis.[1] Within this subgroup of RRMS, some patients have a more aggressive disease course, previously known as "aggressive" MS, now referred to as highly active MS, which is characterized by rapid accumulation of physical or cognitive deficits.[3] Previously known as "aggressive" MS, it is now referred to as highly active MS.[3]

Currently, many patients diagnosed with MS are initiated on disease modifying therapies that are approved in the first line setting. These include disease modifying therapies that may be considered low or moderate efficacy such as interferons or glatiramer acetate. It has been suggested that for patients with highly active disease, there is a need to initiate treatment with higher efficacy drugs to improve long term outcomes. A number of treatments can be trialed for patients with highly active RRMS but additional treatment options with different mechanisms of action and mode of administration are needed. Natalizumab and cladribine were previously reviewed for patients with RRMS but not specifically for those with highly active disease. . This review will evaluate the comparative efficacy and harms of cladribine and natalizumab in adult patients with highly active RRMS

Table 1: Products Available in Canada

Generic Name (Brand Name)	Manufacturer	Formulation	Class	Efficacy
Interferon beta-1b (Betaseron)	Bayer Inc.	Injectable	Immunomodulator	Low
Interferon beta-1a (Avonex, Rebif)	Avonex – Biogen Canada Rebif – EMD Serano	Injectable	Immunomodulator	Low
Peg-interferon beta-1a (Plegridy)	Biogen Canada	Injectable	Immunomodulator	Low
Glatiramer acetate (Copaxone, generics)	Teva Canada Limited	Injectable	Receptor decoy	Low
Teriflunomide (Aubagio, generics)	Sanofi-Aventis Canada	Oral	Pyrimidine synthesis inhibitor	Low
Cladribine (Mavenclad, generics)	EMD Serano	Oral	Adenosine nucleoside analog	Moderate-high
Fingolimod (Gilenya, generics)	Novartis Pharmaceuticals Canada Inc	Oral	S1p inhibitor	Moderate-high
Ponesimod (Ponvory)	Janssen Inc.	Oral	S1p inhibitor	Moderate-high

Siponimod (Mayzent)	Novartis Pharmaceuticals Canada Inc	Oral	S1p inhibitor	Moderate-high
Ozanimod (Zeposia)	Bristol-Myers Squibb Canada	Oral	S1p inhibitor	Moderate-high
Dimethyl fumarate (Tecfidera, generics)	Biogen Canada	Oral	Fumarate	Moderate
Ocrelizumab (Ocrevus)	Hoffmann-La Roche Limited	Injectable	Anti-CD20 monoclonal antibody	High
Ofatumumab (Kesimpta)	Novartis Pharmaceuticals Canada Inc	Injectable	Anti-CD20 monoclonal antibody	High
Natalizumab (Tysabri)	Biogen Canada	Injectable	A4β1-integrin binder	High
Alemtuzumab (Lemtrada)	Sanofi-Aventis Canada	Injectable	Anti-CD52 monoclonal antibody	High

Objectives

The objective of this review is to assess the comparative efficacy and harms of cladribine and natalizumab for the first-line treatment of highly active RRMS.

Policy Question

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

Research Questions

The project will address the following research questions:

1. What is the clinical efficacy and safety of natalizumab and cladribine as first-line treatments in patients with highly active relapsing-remitting multiple sclerosis compared to drugs currently used as first-line treatment in adult patients with highly active RRMS?
2. How do costs compare across disease modifying therapies for the treatment of adult patients with highly active RRMS?

Feedback

CDA-AMC has engaged the following organizations to inform them of the review and initiate a dialogue. These organizations include:

- Canadian Network of MS Clinics (CNMSC)
- MS Society

In addition to the aforementioned outreach with specific organizations, a general call for feedback from all eligible stakeholders will be sought at key stages during this project, including at the time of posting of this project scope (i.e., refer to Status of the Document) and at the following milestones (as communicated through the CDA-AMC Weekly Summary):

- Draft Summary Report
- Draft Recommendation Report
- Proposed revisions to existing recommendations from CDA-AMC's single drug review programs (if applicable)

Methods

This review will leverage a CADTH Health Technology Review that reviewed several drugs for the first line treatment of highly active RRMS. An information specialist will update 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, to identify new evidence since the publication of the report (Table 2).[4]

Table 2: Systematic Review Selection Criteria

Criteria	Description
Population	DMT-naïve adults with highly active relapsing MS Potential Subgroups • age at diagnosis (e.g., 18 years to < 50 years; ≥ 50 years) • Time since diagnosis (to account for disease duration) • EDSS score (e.g., < 3; 3 to < 6; ≥ 6) • MRI activity at baseline
Interventions	Cladribine 3.5mg/kg orally over 2 years, administered as 1 treatment course of 1.75mg/kg per year Natalizumab 300mg IV infusion every 4 weeks
Comparators	Relapsing MS first-line therapies:[a] • Interferons (interferon beta-1A, interferon beta-1B) • Glatiramer acetate • Dimethyl fumarate • Teriflunomide • Ocrelizumab • Ofatumumab
Outcomes	**Efficacy:** • Relapses (e.g., relapse rate, relapse-free rate, time to relapse) • Disability progression (including time to progression) or improvement • Function (e.g., MSFC score including T25-FW, or 9-HPT individual scores) • Imaging outcomes (e.g., MRI brain lesions, MRI brain volume, spinal cord imaging) • Cognitive outcomes (e.g., MSNQ, PASAT 3, SDMT) • Symptoms (e.g., fatigue, cognition, mobility, visual disturbance)

Criteria	Description
	• HRQoL (e.g., MSQOL-54, MSQLI, MS-QLQ27) • Instrumental activities of daily living (e.g., absenteeism, presentism, employment status) **Safety:** • Adverse events • Serious adverse events • Withdrawal due to adverse events • Mortality • Notable harms: injection-related reactions, opportunistic infections, serious infections, progressive multifocal leukoencephalopathy, lymphopenia, neutropenia, malignancies
Study design	Published phase II, phase III and phase IV RCTs If no RCTs are available to adequately inform the research question: comparative prospective cohort studies
Search dates	TBD

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

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

Stakeholder Input

CDA-AMC will summarize input received from all groups within the Summary Report and Recommendations Report.

Economic Analysis

A cost comparison table will be developed using list prices from a public drug plan incorporating the dosing regimens as described within the respective Product Monographs.

Process

The project will be conducted in accordance with the *Procedures for* CDA-AMC Streamlined Reviews. This will include the development of recommendations or advice from the CDA-AMC Formulary Management Expert Committee (FMEC) and may include updates to previous reimbursement review recommendations that have been issued by CDA-AMC in this therapeutic area.

Status of the Document

This proposed project scope is posted for 10 business days as of the date of this posting for stakeholder feedback. The feedback will be considered as the project plan is finalized.

References

1. Haki M, Al-Biati HA, Al-Tameemi ZS, Ali IS, Al-Hussaniy HA. Review of multiple sclerosis: Epidemiology, etiology, pathophysiology, and treatment. *Medicine (Baltimore).* 2024;103(8):e37297.
2. Baskaran AB, Grebenciucova E, Shoemaker T, Graham EL. Current Updates on the Diagnosis and Management of Multiple Sclerosis for the General Neurologist. *J Clin Neurol.* 2023;19(3):217-229.
3. Diaz C, Zarco LA, Rivera DM. Highly active multiple sclerosis: An update. *Mult Scler Relat Disord.* 2019;30:215-224.
4. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol.* 2016;75:40-46.