Drug Benefit Council (DBC) Recommendation and Reasons for Recommendation

FINAL

Therapeutic Review
Drugs for Treatment of Multiple Sclerosis (MS)
Various Manufacturers

Description:

The purpose of the therapeutic review was to review medications for the treatment of multiple sclerosis (MS). The Ministry of Health (the Ministry) identified the need to review tiering of therapies and for a review of the current criteria for PharmaCare coverage because it is based on the 2010 McDonald diagnostic criteria, which was revised in 2017. In addition, MS specialists asked the Ministry to review whether age could be used as criteria for treatment discontinuation.

In their review, the DBC considered the following: a 2019 presentation on the Expanded Disability Status Scale (EDSS); a document summarizing the differences between the 2010 and 2017 McDonald criteria; a 2018 editorial from the *Multiple Sclerosis Journal* titled "McDonald MS diagnostic criteria: Evidence-based revisions" (Vol. 24[2] 92 –95); a 2019 presentation by the Drug Assessment Working Group (DAWG) of the Therapeutics Initiative (TI), UBC on the McDonald Criteria for Multiple Sclerosis; the July 2020 Main Report, the Final Report on evidence to support discontinuation of MS drug therapies in older patients with relapsing remitting multiple sclerosis (RRMS), and the Executive Summary of the systematic review comparing drugs funded in British Columbia to treat RRMS by the DAWG of the TI, UBC; Clinical Practice Reviews from two specialists; Patient Input Questionnaire responses from 172 patients and 4 caregivers; and a Budget Impact Assessment.

Dosage Forms:

Interferon beta-1a (Rebif) 22 mcg (6 MIU) and 44 mcg (12 MIU) pre-filled syringe
Interferon beta-1a (Avonex) 30 mcg/0.5 mL (6 MIU) pre-filled syringe
Interferon beta-1b (Extavia) 0.3 mg (9.6 MIU) powder for injection single use vial
Interferon beta-1b (Betaseron) 0.3 mg single use vial
Dimethyl fumarate (Tecfidera) 120 mg capsule
Glatiramer acetate (Glatect) 20 mg/mL pre-filled syringe
Teriflunomide (Aubagio) 14 mg tablet
Riximyo (rituximab) 10 mg/mL vial
Ruxience (rituximab) 10 mg/mL vial
Truxima (rituximab) 10 mg/mL vial

Alemtuzumab (Lemtrada) 12 mg/1.2 mL vial
Fingolimod (generics) 0.5 mg capsule
Natalizumab (Tysabri) 300 mg/15mL vial
Cladribine (Mavenclad) 10 mg tablet
Ocrelizumab (Ocrevus) 30 mg/mL single-use vial containing 300 mg
Peginterferon beta-1a (Plegridy) 125 mcg/0.5 mL pre-filled syringe

Recommendations:

1. Based on the evidence provided, what is your recommendation to the British Columbia Ministry of Health (the Ministry) regarding adopting the 2017 McDonald diagnostic criteria for multiple sclerosis by PharmaCare for the diagnosis and initiation of treatment of disease modifying drugs for all subtypes of MS? (Currently the 2010 McDonald diagnostic criteria for MS is being used).

    a. The DBC recommends that that the Ministry should adopt the 2017 McDonald diagnostic criteria for the diagnosis and initiation of treatment of disease-modifying drugs for all subtypes of MS.

    Rationale: well-supported evidence from clinical studies indicates that by applying the 2017 McDonald criteria, MS can be diagnosed more frequently at the time of first clinical event as compared to the 2010 McDonald criteria.

        1.) The presence of oligoclonal bands in cerebrospinal fluid (CSF) can be used as an alternative to dissemination of lesions in time (DIT) to establish MS in patients with clinically isolated syndrome (CIS) and MRI or clinical evidence of dissemination of lesions in space (DIS). This is the main driver of increased MS diagnoses in patients that previously presented as a CIS.
        2.) Other changes to the 2010 McDonald criteria made them easier to apply, include grouping both symptomatic and asymptomatic lesions of brainstem or spinal cord to demonstrate DIS or DIT in patients with supra-tentorial, infra-tentorial or spinal cord lesions. Cortical lesions were also added to juxta cortical lesions for use in MRI criteria to demonstrate DIS.
        3.) The changes to the McDonald criteria increase the diagnosis of MS by ~30% and decrease the mean time to clinically definite MS diagnosis from ~6 to ~2 months.
        4.) PharmaCare should not base its coverage criteria on a specific year of the McDonald criteria but instead should use the current criteria.

2. Currently British Columbia PharmaCare does not have a specific threshold for discontinuing ongoing disease modifying therapies. Based on the available evidence provided, what is the drug coverage strategy recommended to the British Columbia PharmaCare for discontinuing therapy after the age of 55 or 65 years old?

a. The DBC finds that there is not enough evidence to make a recommendation regarding discontinuation criteria based on age.
b. The DBC recommends that age, taken in isolation, should not be the determining factor for renewal criteria; however, age may be considered among several other criteria (e.g. possibly disease status, radiographic imaging, symptoms, etc.) that may prompt a review of coverage.

Rationale: the systematic review identified no randomized controlled trials (RCTs) that examined the role of continuing or stopping MS treatment(s) based on age less than 60 years as compared to 60 years and older.

1.) No RCT was identified that examined the role of continuing or stopping MS treatments based on age less than 60 compared to 60 years and older.
2.) Two observational studies in patients aged over 55 years were identified. In one retrospective study, patients and providers were allowed to discontinue treatment, which introduced selection bias. Also, a large number of patients had missing data, which limited more detailed analysis. The second study used simulation modeling suggested the benefits of MS drug therapies may not be substantial among older adults with RRMS, however also highlighted the lack of direct clinical evidence and importance of patient preferences.

3. What is the comparative effectiveness and safety of disease-modifying therapies to treat Relapsing Remitting Multiple Sclerosis (RRMS)?

a. The DBC was not provided sufficient evidence on the comparative effectiveness and safety of disease-modifying therapies for RRMS and therefore was not able to recommend any changes to coverage at this time.

Rationale: there is insufficient comparative evidence of efficacy from clinical trials to recommend one treatment over another. Head-to-head RCTs and network meta-analyses of MS drugs had numerous limitations, which are listed below.

1.) The TI report identified 27 RCTs that examined 35 comparisons of one MS drug to another in adult patients with RRMS. However, the number of head-to-head comparisons were limited. A majority of the trials were against interferon beta-1a and glatiramer acetate; no RCTs compared oral MS drugs to one another; no RCTs compared newer biologic MS drugs to one-another and no RCTs compared an oral MS drug to a newer biologic drug.
2.) The TI report recommended that a network meta-analysis cannot be used due to the heterogeneity of existing trials, including differences

in diagnostic criteria, follow-up period and endpoints that also limit the utility of a network meta-analysis for this purpose.

3.) The DBC requested additional evidence from studies and guidelines as part of the evidence package. If the Ministry decides to broaden its review to observational studies, or network meta-analyses, the DBC is willing to assist in this review.

Of Note:

- Patient and caregiver responses to the Patient Input Questionnaire indicated that RRMS has significant impacts on their day-to-day lives. Patients reported a variety of physical, cognitive and emotional impacts, including mobility issues, fatigue, decreased balance, numbness and tingling, vertigo, physical pain, muscle tremors, vision issues, bladder problems, difficulty remembering and concentrating, anxiety due to the unpredictable nature of disease, and depression.
- Patients had been prescribed a variety of treatments, with more than half of respondents reporting they had tried more than one drug. Patients indicating there is a wide range of individual response to these treatments, as well as a wide range of tolerability (i.e. patients reported having difficulty tolerating every one of the drugs listed, with the interferons reportedly being the most difficult to tolerate).
- Patients hoped for MS treatments that would halt the progression of the disease and that would enable some recovery from MS symptoms. Patients also hoped for treatments that were more tolerable or less burdensome (i.e. many patients expressed a preference for oral treatments rather than injections or infusions).
- A common theme in the responses is that no one MS treatment is effective or tolerable for all patients.