BRITISH COLUMBIA | Ministry of Health

Drug Coverage Decision for B.C. PharmaCare

About PharmaCare B.C. PharmaCare is a government-funded drug plan. It helps British Columbians with the cost of eligible prescription drugs and specific medical supplies.

Details of Drug Reviewed

Drug	**cladribine**
Brand Name	Mavenclad®
Dosage Form(s)	10 mg oral tablet
Manufacturer	EMD Sereno
Submission Type	**New Submission**
Use Reviewed	Relapsing Remitting Multiple Sclerosis (RRMS)
Common Drug Review (CDR)	Yes, CDR recommended: **to Reimburse with clinical criteria and/or conditions**. Visit the CDR website for more details: www.cadth.ca/node/88649.
Drug Benefit Council (DBC)	The DBC met on December 3, 2018. and considered the following: the final reviews completed by the Common Drug Review (CDR) on October 24, 2018, which included clinical and pharmacoeconomic evidence review material and the recommendations from the Canadian Drug Expert Committee (CDEC). The DBC also considered Patient Input Questionnaire responses from two patients and one Patient Group, patient input provided to the CDR, a Clinical Practice Review from one specialist, an Other Drug Agencies Review Recommendations (ODARR) document from the Canadian Agency for Drugs and Technologies in Health, and a Budget Impact Assessment.
Drug Coverage Decision	**Limited Coverage Benefit** **Access the cladribine criteria from www.gov.bc.ca/pharmacarespecialauthority**
Date	January 25, 2022

Reason(s)	**Drug coverage decision is consistent with the CDEC recommendation, but not consistent with DBC recommendation.** • One double-blind randomized controlled trial comparing cladribine with placebo in a population of patients with RRMS found it was superior for reducing annualized relapse rates and was associated with a decreased risk of confirmed disease progression. • The DBC recommended not to fund based on discrepancy between the clinical trial which used cladribine in patients not previously on therapy and Health Canada's indication to use in patients that have already tried at least one treatment option. However, based on various inputs, it was determined that some patients may benefit from cladribine. • The pan-Canadian Pharmaceutical Alliance was successful in addressing the Ministry of Health's concerns on cost and cost effectiveness.
Other Information	DBC Final Recommendations attached.

The Drug Review Process in B.C.

A manufacturer submits a request to the Ministry of Health (Ministry).

An independent group called the Drug Benefit Council (DBC) gives advice to the Ministry. The DBC looks at:

- whether the drug is safe and effective
- advice from a national group called the Common Drug Review (CDR)
- what the drug costs and whether it is a good value for the people of B.C.
- ethical considerations involved with covering or not covering the drug
- input from physicians, patients, caregivers, patient groups and drug submission sponsors

The Ministry makes PharmaCare coverage decisions by taking into account:

- the existing PharmaCare policies, programs and resources
- the evidence-informed advice of the DBC
- the drugs already covered by PharmaCare that are used to treat similar medical conditions
- the overall cost of covering the drug

Visit The Drug Review Process in B.C. - Overview and Ministry of Health - PharmaCare for more information.

This document is intended for information only.
It does not take the place of advice from a physician or other qualified health care provider.

Drug Benefit Council (DBC) Recommendation and Reasons for Recommendation

FINAL

Cladribine (Mavenclad™)

EMD Serono, a Division of EMD Inc., Canada

Description:

Drug review of **cladribine (Mavenclad™)** for the following Health Canada approved indications:

For the treatment of relapsing remitting multiple sclerosis (RRMS).

In their review, the DBC considered the following: the final reviews completed by the Common Drug Review (CDR) on October 24, 2018, which included clinical and pharmacoeconomic evidence review material and the recommendations from the Canadian Drug Expert Committee (CDEC). The DBC also considered Patient Input Questionnaire responses from two patients and one Patient Group, patient input provided to the CDR, a Clinical Practice Review from one specialist, an Other Drug Agencies Review Recommendations (ODARR) document from the Canadian Agency for Drugs and Technologies in Health, and a Budget Impact Assessment.

Dosage Forms:

Mavenclad™ is available as cladribine 10 mg tablet.

Recommendations:

The Drug Benefit Council (DBC) recommends that **Cladribine (Mavenclad™)** not be listed.

Of Note:

- A therapeutic review of drugs for the treatment of RRMS is warranted, as there are now many drugs in this class.

Reasons for the Recommendation:

1. Summary

- One double-blind randomized controlled trial (RCT) comparing cladribine with placebo in a population of patients with RRMS found it was superior to placebo for reducing annualized relapse rates and was associated with a decreased risk of confirmed disease progression sustained for three months.
- There is a discrepancy between the Health Canada approved indication (as a second-line therapy following an inadequate response to or inability to tolerate one or more therapies for RRMS) and the population in the trial, which was treatment-naïve.
- There was a lack of health-related quality of life and symptom data in the trial, and there is a lack of comparative data for cladribine versus the many other disease-modifying therapies for MS.
- Higher proportions of patients treated with cladribine in the trial experienced certain notable adverse events (i.e. lymphopenia, herpes zoster infection, and neoplasms) than placebo. There is a lack of comparative safety data for cladribine versus other disease-modifying therapies for MS.
- At the manufacturer submitted price, cladribine is significantly more expensive than other disease-modifying therapies for MS, and without a significant price reduction it is unlikely to be a cost-effective treatment for patients with RRMS.

2. Clinical Efficacy

- The DBC considered the CDR Clinical Review, which included one double-blind RCT (the CLARITY trial) that compared two different dose regimens of cladribine (3.5 mg/kg or 5.25 mg/kg, which is not the approved dose for cladribine) with placebo in a population of patients with RRMS.
- The Health Canada indication for cladribine generally recommends it 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.
- The primary outcome in CLARITY was the annualized relapse rate. Other outcomes included disability progression, MRI outcomes, health-related quality of life, and freedom from disease activity.

- Cladribine was superior to placebo for reducing annualized relapse rates and was associated with a decreased risk of confirmed disease progression sustained for three months as compared with placebo.
- Key efficacy outcomes such as disability progression and health-related quality of life were not adjusted for multiple comparisons, and there was a significant amount of missing data for the health-related quality of life outcomes.
- The lack of health-related quality of life and data is an important limitation in a condition characterized by significant symptoms and quality of life issues.
- As CLARITY was a placebo-controlled trial, there is a lack of comparative data for cladribine versus many other disease-modifying therapies for MS.
- For detailed information on the systematic review of cladribine (Mavenclad™) please see the CDEC Final Recommendation at: https://www.cadth.ca/cladribine.

3. Safety

- A numerically higher proportion of cladribine patients reported an adverse event over the 96-week CLARITY study, and there was no notable difference in patients with a serious adverse event between groups.
- Lymphopenia was a common adverse event and occurred numerically more frequently with cladribine than with placebo. 2% of cladribine patients developed herpes zoster versus none in the placebo group.
- There are no long-term comparative safety data for oral cladribine.
- 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. 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 detailed information on the safety and tolerability of cladribine (Mavenclad™) please see the CDEC Final Recommendations at the links above.

4. Economic Considerations

- At the manufacturer-submitted price, cladribine is significantly more expensive than other drugs indicated for the treatment of RRMS, including the interferons (interferon beta-1a, interferon beta-1b, peginterferon beta-1a), daclizumab, glatiramer, alemtuzumab, natalizumab, rituximab (an off-label indication), ocrelizumab, dimethyl fumarate, fingolimod, and teriflunomide.
- The CDR reanalysis of the manufacturer-submitted cost-utility analysis found that, based on conventionally accepted thresholds, cladribine was not a cost-effective treatment for patients with RRMS either in the total population or in the specific subpopulations considered.

5. Of Note

- Two patients and one Patient Group responded to the request for patient input. No patients had tried cladribine. Patient input indicated that people with MS experience a wide variety and severity of symptoms, most commonly difficulty in walking, visual impairment, cognitive difficulties, depression, bladder problems, and pain.
- Patient response to MS treatments is highly individual, and no one treatment works for all patients.