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	**siponimod**
Brand Name	Mayzent™
Dosage Form(s)	0.25 mg film-coated tablet 2 mg film-coated tablet
Manufacturer	Novartis Pharmaceuticals Canada Inc.
Submission Type	**New Submission**
Use Reviewed	Secondary progressive multiple sclerosis (SPMS)
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 Drug Benefit Council (DBC) met on August 10, 2020, and considered various inputs including: the final reviews completed by the Common Drug Review (CDR) on July 21, 2020, 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 10 patients and one patient groups, patient input provided to the CDR, a Clinical Practice Reviews from one specialist, and a Budget Impact Analysis.
Drug Coverage Decision	**Limited Coverage Benefit** **Access the siponimod criteria from www.gov.bc.ca/pharmacarespecialauthority**
Date	January 25, 2022

Reason(s)	• **Drug coverage decision is consistent with CDEC and DBC recommendations:** ○ Results from one double-blind, phase III, randomized controlled trial (EXPAND) in patients with and without active SPMS who were treated with siponimod demonstrated a clinically meaningful benefit compared with placebo in reducing the time to three-month confirmed disability progression. Results from EXPAND suggest that siponimod may also provide benefit in preventing relapses and improving imaging outcomes. ○ The Ministry participated in the pan-Canadian Pharmaceutical Alliance negotiations with the manufacturer which was able to address the concerns identified by the CDEC and DBC with respect to value for money.
Other Information	DBC Recommendations & Reasons (R&R) 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

Siponimod (Mayzent™)

Novartis Pharmaceuticals Canada Inc.

Description:

Drug review of **siponimod (Mayzent™)** for the following Health Canada approved indication(s):

For the management of secondary progressive multiple sclerosis (SPMS) in adults.

In their review, the DBC considered the following: the final reviews completed by the Common Drug Review (CDR) on July 21, 2020, 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 10 patients and one patient groups, patient input provided to the CDR, a Clinical Practice Reviews from one specialist, and a Budget Impact Assessment.

Dosage Forms:

Mayzent™ is available as siponimod 0.25 mg and 2 mg tablet.

Recommendations:

1. The Drug Benefit Council (DBC) recommends that siponimod (Mayzent™) not be listed at the submitted price.
2. If a significant price reduction is achieved, the DBC recommends the following coverage criteria:

Initiation Criteria

1. Patients who have all of the following characteristics:
   1.1. a history of relapsing-remitting multiple sclerosis (RRMS) and current active SPMS;
   1.2. an Expanded Disability Status Scale (EDSS) score of 3.0 to 6.5; and
   1.3. documented EDSS progression during the two years prior to initiating treatment with siponimod (≥ 1 point if EDSS < 6.0; ≥ 0.5 points if EDSS ≥ 6.0 at screening).
2. Siponimod should not be used in combination with other disease-modifying treatments (DMTs) used to treat multiple sclerosis (MS).

Renewal Criteria

1. Patients should be assessed for a response to siponimod every six months.
2. Siponimod may be renewed for patients who do not exhibit evidence of disease progression since the previous assessment. Disease progression is defined as an increase in the EDSS score of ≥ 1 point if the EDSS score was 3.0 to 5.0 at siponimod initiation, or an increase of 5.5 to 6.5 at siponimod initiation.

Discontinuation Criteria

1. Treatment with siponimod should be discontinued in patients who exhibit either of the following:
1.1. progression to an EDSS score of equal to or greater than 7.0 at any time during siponimod treatment; or
1.2. confirmed worsening of at least 20% on the timed 25-foot walk since initiating siponimod treatment.

Prescribing Conditions

1. The patient is under the care of a specialist with experience in the diagnosis and management of MS.

Reasons for the Recommendation:

1. Summary

- Results from one double-blind, phase III, randomized controlled trial (EXPAND) in patients with and without active SPMS who were treated with siponimod 2 mg daily demonstrated a clinically meaningful benefit compared with placebo in reducing the time to three-month confirmed disability progression (CDP). Results from EXPAND suggest that siponimod may also provide benefit in preventing relapses and improving imaging outcomes.
- The observed benefits in the subgroup of patients with active SPMS were generally consistent with the overall study population (with and without active SPMS); however, the magnitude of the treatment effect of siponimod was more evident in the active SPMS subgroups.

- The estimated incremental cost-effectiveness ratio (ICER) for siponimod compared with best supportive care (BSC) was $194,007 per quality-adjusted life-year (QALY). CADTH estimated a price reduction of at least 63% would be required to achieve an ICER below a willingness-to-pay threshold of $50,000 per QALY.

2. Clinical Efficacy

- The DBC considered the CADTH systematic review, which included one double-blind, randomized, event-driven, exposure-driven, phase III, placebo-controlled trial (EXPAND) in patients with SPMS. EXPAND was conducted in patients with a broad range of SPMS phenotypes, but the indication approved by Health Canada is limited to patients with SPMS, defined as patients with active disease evidenced by relapses or imaging features characteristic of multiple sclerosis inflammatory activity, to delay the progression of physical disability.
- Outcomes in EXPAND included the following: disability progression, health-related quality of life (HRQoL), mobility, relapse-related outcomes, and imaging outcomes. The primary outcome in EXPAND was time to three-month CDP based on the EDSS score. Outcomes related to fatigue were not assessed in EXPAND and cognitive function was not assessed in the active SPMS population specifically.
- Patients treated with siponimod 2 mg daily demonstrated a clinical benefit compared to placebo in reducing the time to 3-month CDP at month 12 based on a clinically minimal important change of EDSS score. Further, results from EXPAND suggest that siponimod may provide benefit in preventing relapses and on improving imaging outcomes.
- No impact on patient's mobility was observed in EXPAND, and there is uncertainty regarding the improvement of disease-related symptoms and HRQoL. The observed benefits were generally consistent between the subgroup of active SPMS and the overall study population; however, the magnitude of the treatment effect of siponimod was more evident in the active SPMS subgroups.
- There is no evidence from EXPAND to support a potential benefit of siponimod in combination with immunomodulatory therapies or DMTs for multiple sclerosis as concomitant administration of such treatments was not permitted in the trial.
- For detailed information on the systematic review of siponimod please see the CDEC Final Recommendation at: https://www.cadth.ca/siponimod.

3. Safety

- Adverse events (AEs) were overall higher among patients treated with siponimod (88.7%) than with placebo (81.5%). The incidence of specific AEs was similar between the two treatment groups, although hypertension, nausea, alanine aminotransferase increase, and peripheral edema were slightly more common for patients treated with siponimod.
- Serious AEs were reported by 17.9% of patients treated with siponimod and 15.2% of patients treated with placebo.
- The proportions of withdrawal due to AEs were low (7.6% for siponimod versus 5.1% for placebo). Macular edema was the most common AE leading to withdrawal from treatment, occurring in 1.0% of those treated with siponimod and one patient treated with placebo.
- Bradycardia and macular edema were identified as notable harms in the CADTH review protocol and were more common in the siponimod group compared with the placebo group (4.5% versus 2.6% and 1.6% versus 0.2%, respectively). Four deaths from each treatment group were reported during EXPAND.
- For detailed information on the safety and tolerability of siponimod, please see the CDEC Final Recommendations at the links above.

4. Economic Considerations

- The DBC considered the CADTH reanalysis of the manufacturer's economic submission, which consisted of a cost-utility analysis comparing siponimod, interferons (Extavia, Rebif, Avonex, Betaseron), natalizumab, and BSC for patients with active SPMS. The CADTH reanalysis reported that siponimod was associated with incremental QALYs of 0.75 and incremental health care costs of $146,424, leading to an ICER of $194,007 per QALY when compared with BSC.
- At a $50,000-per-QALY threshold, a 63% price reduction would be needed for siponimod to be considered cost-effective.

5. Of Note

- The DBC considered patient input received from 10 patients and 1 patient group. Patient input indicated that MS has an enormous impact on every aspect of a patient's daily life as well as on the daily lives of family, caregivers, and community. The SPMS phase of MS is characterized by irreversible disability progression.
- Patients reported using numerous other drugs for treatment of MS, although some noted that siponimod is the only treatment specifically approved for SPMS. One patient reported having tried siponimod, as part of a clinical trial; this patient reported the drug stopped their disease progression and lesion development and greatly increased their energy.
- Patients and the patient group emphasized the need for siponimod as a treatment specifically approved for SPMS.