Drug Coverage Decision for B.C. PharmaCare

About PharmaCare

Drug	**letermovir**
Brand Name	Prevymis®
Dosage Form(s)	240 mg and 480 mg oral tablets
Manufacturer	Merck Canada Inc.
Submission Type	**New Submission**
Use Reviewed	For the prophylaxis of cytomegalovirus (CMV) infection.
Common Drug Review (CDR)	Yes, CDR recommended: **to Reimburse with clinical criteria and/or conditions**. Visit the CDR website for more details: https://www.cadth.ca/sites/default/files/cdr/complete/SR0545_cdr_complete_Prevymis_June_22_2018.pdf
Drug Benefit Council (DBC)	The DBC met on July 9, 2018, and considered various inputs including: the final reviews completed by the Common Drug Review (CDR) on June 20, 2018, which included clinical and pharmacoeconomic evidence review material and the recommendations from the Canadian Drug Expert Committee (CDEC). The DBC received no Patient Input Questionnaire responses, and so responses to the CDR Patient Input were used, as well as an Other Drug Agencies Review Recommendations document from the Canadian Agency for Drugs and Technologies in Health (CADTH) and a Budget Impact Assessment.
Drug Coverage Decision	**Limited Coverage Benefit. Access the letermovir criteria from www.gov.bc.ca/pharmacarespecialauthority**
Date	May 18, 2021
Reason(s)	**Drug coverage decision is consistent with the CDEC and DBC recommendations.**

	• CDEC and DBC recommended that letermovir be reimbursed for the prophylaxis of CMV infection in adult CMV-seropositive recipients (R+) of an allogeneic hematopoietic stem cell transplant (HSCT). The DBC indicated that the Ministry should develop criteria in identifying the appropriate population of HSCT recipients who are considered to be at high risk of CMV infection. • Letermovir demonstrated some advantages to placebo in the reduction in clinically significant CMV infection 24 weeks after transplant and was similar to placebo with respect to safety. • Based on economic considerations and the submitted product price, the cost-effectiveness for letermovir was uncertain compared to the standard approach to CMV management using pre-emptive antiviral therapy. CDEC indicated that a reduction in price is likely to increase the probability that letermovir is cost-effective for all patients who meet the Health Canada–approved indication. • The Ministry participated in the pan-Canadian Pharmaceutical Alliance (pCPA) negotiations with the manufacturer which were able to address the concerns identified by the CDEC and DBC with respect to the cost-effectiveness and value for money for letermovir.
Other Information	None

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

letermovir (Prevymis™)
Merck Canada Inc.

Description:

Drug review of **letermovir (Prevymis™)** for the following Health Canada approved indications:

> For the prophylaxis of cytomegalovirus (CMV) infection in adult CMV-seropositive recipients (R+) of an allogeneic hematopoietic stem cell transplant (HSCT).

In their review, the DBC considered the following: the final reviews completed by the Common Drug Review (CDR) on June 20, 2018, which included clinical and pharmacoeconomic evidence review material and the recommendations from the Canadian Drug Expert Committee (CDEC). The DBC received no Patient Input Questionnaire responses, and so responses to the CDR Patient Input site were used, as well as an Other Drug Agencies Review Recommendations document from the Canadian Agency for Drugs and Technologies in Health (CADTH) and a Budget Impact Assessment.

Dosage Forms:

Prevymis™ is available as letermovir 240 mg and 480 mg oral tablets, and letermovir 20 mg/mL, 240 mg/vial and 480 mg/vial IV solution for injection.

Recommendations:

1. The Drug Benefit Council (DBC) recommends that letermovir be listed as a benefit for the prophylaxis of CMV infection in adult CMV-seropositive recipients [R+] of an allogeneic HSCT, with the following conditions:
    a. The patient is under the care of clinicians with expertise in the management of HSCT.
    b. There should be a substantial reduction in price.

Of Note:

- The ministry will develop criteria to assist in identifying the appropriate population of HSCT recipients who are considered to be at high risk of CMV infection.

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Reasons for the Recommendation:

1. Summary

- One double-blind, placebo-controlled, randomized controlled trial (RCT) using letermovir as a prophylactic treatment strategy for the prevention of CMV infection in adult CMV-seropositive recipients (R+) of an allogeneic HSCT resulted in a statistically significant and clinically meaningful reduction in the primary end point of clinically significant CMV infection at 24 weeks post-transplant.
- Letermovir is a novel agent for prophylaxis of CMV. Other agents are used either as pre-emptive therapy (PET) or as treatments of active CMV.
- The addition of letermovir as prophylaxis alongside usual care in adult CMV seropositive HSCT recipients resulted in an incremental cost-utility ratio (ICUR) of $51,052 per quality adjusted life year (QALY) gained compared to usual care alone.

2. Clinical Efficacy

- The DBC considered the CDR clinical review, which included one phase III double-blind, placebo-controlled, multi-centre, multinational, superiority RCT (Study P001), which was designed to evaluate the efficacy and safety of letermovir as a preventive strategy for CMV infection in adults who are CMV-seropositive recipients (R+) of an allogeneic HSCT 24 weeks post-transplant.
- The primary efficacy endpoint of Study P001 was the incidence of clinically significant CMV infection through week 24 post-transplant defined as the occurrence of either CMV end-organ disease, or initiation of anti-CMV PET based on documented CMV viremia and the clinical condition of the patient.
- Secondary outcomes included clinically significant CMV infection through week 14 post-transplant, initiation of PET as well as time to initiation of PET and CMV end-organ disease as well as time to onset of CMV end-organ disease. Exploratory endpoints included mortality, opportunistic bacterial and/or fungal infections, graft versus host disease (GVHD), re-hospitalization, quality of life and genotypic variance and resistance.
- Letermovir was associated with a statistically significant reduction in clinically significant CMV infection at week 24 post-transplant (the primary outcome) using the primary method for imputing data (non-completers and missing data were considered to have met the primary end point).
- Overall, the results of the secondary outcomes were also consistent with the primary analysis in the reduction of clinically significant CMV infection; however no adjustments for multiple statistical testing were made for any outcomes other than the primary analysis of the primary endpoint. The frequency of all-cause mortality, all-cause mortality in patients meeting the primary end point, and non-relapse related mortality was lower in the letermovir group compared with the placebo group through week 14, week 24, and week 48 post-transplant.

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- Time to onset of clinically significant CMV infection through week 24 post-transplant was also evaluated as a secondary outcome using Kaplan-Meier (KM) methods. An increase in the KM rate of events can be observed between weeks 14 and 24 in the letermovir group only. Therefore, the time to event endpoints evaluated in Study P001 may suggest a potential increase in clinically significant CMV infection when patients are no longer treated with letermovir. Study P001 does not provide any data to assess the safety and efficacy of letermovir beyond 14 weeks.
- For detailed information on the systematic review of letermovir (Prevymis), please see the CDEC Final Recommendation at: https://www.cadth.ca/sites/default/files/cdr/complete/SR0545_cdr_complete_Prevymis_June_22_2018.pdf.

3. Safety

- In Study P001 a similar proportion of patients in the letermovir group experienced adverse events and serious adverse events compared to the placebo group through week 14, 24 and 48 post-transplant. A greater frequency of treatment withdrawal due to adverse events was reported in the placebo group compared to the letermovir group, which may be attributed to a higher proportion of patients discontinuing due to CMV infection.
- The occurrence of notable harms was approximately equivalent in both treatment groups through week 14, 24 and 48 post-transplant. Overall, more patients experienced cardiac disorders through week 14 post-transplant in the letermovir group compared to the placebo group. The most common reasons for cardiac disorders were atrial fibrillation, sinus tachycardia and tachycardia. The differences between the two groups diminished through week 24 and 48 post-transplant.
- For detailed information on the safety and tolerability of letermovir (Prevymis), please see the CDEC Final Recommendations at the link above.

4. Economic Considerations

- The CDR found it difficult to determine the cost-effectiveness of letermovir used as a prophylactic treatment strategy compared with usual care because it is uncertain how letermovir will be used in practice, and what its long-term effects are on mortality.
- The CDR reanalysis of the manufacturer's submission resulted in an ICUR for letermovir with usual care of $51,052 per QALY gained compared with usual care alone.

5. Of Note

- No patient input was received. Patient input to the CDR process was unclear as to whether any respondents had experienced CMV or whether any patients had used letermovir.
- Letermovir has only been studied as in primary prophylaxis of CMV, and there is currently no data on how to use letermovir for therapy of active CMV (viremia or

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disease) in terms of dosing or efficacy. letermovir should not be used for PET at the present time.

- Letermovir may have the potential for off-label use in the prophylaxis of CMV in patients receiving solid organ transplants or in patients who are considered at risk for a recurrent CMV infection.

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