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CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

LETERMOVIR (PREVYMIS — MERCK CANADA INC.)
Indication: Cytomegalovirus infection, prophylaxis

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that letermovir be reimbursed for the prophylaxis of cytomegalovirus (CMV) infection in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT), if the following conditions are met:

Conditions
- Patient is under the care of clinicians with expertise in the management of HSCT.
- Reduction in price.

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LETERMOVIR (PREVYMIS — MERCK CANADA INC.)

Indication: Cytomegalovirus infection, prophylaxis

Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that letermovir be reimbursed for the prophylaxis of cytomegalovirus (CMV) infection in adult CMV-seropositive recipients (R+) of an allogeneic hematopoietic stem cell transplant (HSCT), if the following conditions are met:

Conditions:

- Patient is under the care of clinicians with expertise in the management of HSCT.
- Reduction in price.

Reasons for the Recommendation:

1. In one double-blind, placebo-controlled, randomized controlled trial (RCT) (Study P001; N = 570), letermovir used 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.
2. The cost-effectiveness of letermovir used as a prophylactic treatment strategy compared with usual care is difficult to determine because it is uncertain how letermovir will be used in practice and what the long-term effects of letermovir are on mortality — effects that could not be explored adequately in the economic model. Depending on the mortality benefit assumed with letermovir, the cost-effectiveness of letermovir could range from being dominated (i.e., more costly and less effective) to an incremental cost-utility ratio (ICUR) of $19,339 per quality-adjusted life-year (QALY) when compared with usual care. Due to these limitations, the committee cannot provide guidance on the per cent price reduction required for letermovir to be considered a cost-effective treatment strategy. 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.

Of Note:

- Clinical experts with experience in treating patients undergoing HSCT indicated that letermovir would likely be used in patients who are considered to be at high risk of CMV infection. The clinical experts suggested that high-risk patients would include:
    - umbilical cord blood transplant recipients
    - haploidentical recipients
    - recipients of T-cell depleted grafts
    - recipients requiring high-dose steroids or other immunosuppression for acute graft-versus-host disease (GVHD).

  The clinical experts emphasized that developing a comprehensive definition of patients considered at high risk of CMV infection would be difficult. Most patients enrolled in Study P001 appeared to be at low risk of CMV infection, and considering the limitations of the subgroup analyses conducted, CDEC was unable to provide further guidance on reimbursement criteria that would be appropriate to limit the use of letermovir to high-risk patients. Should participating drug plans elect to restrict access to patients most likely to benefit from letermovir treatment, thereby increasing the likelihood of letermovir being a cost-effective treatment option, reimbursement criteria should be developed at a jurisdictional level in consultation with clinical experts.

Discussion Points:

- CDEC noted that there is the potential for letermovir to be used off-label for patients who are considered at risk for a recurrent CMV infection. Although letermovir may have efficacy when used in such situations, it has not been studied for this indication. There is also the potential for letermovir to be used off-label for patients requiring therapy who are refractory or resistant to ganciclovir or valganciclovir. Letermovir may potentially be less toxic than currently available alternatives (i.e., foscarnet, cidofovir) but its relative efficacy is unknown.
- CDEC noted that there was an increase in clinically significant CMV infection in the letermovir treatment group based on time to onset of clinically significant CMV infection between weeks 14 and 24 post-transplant in Study P001. These results suggest a potential increase in clinically significant CMV infection when patients are no longer treated with letermovir, implying that there may be some uncertainty in the durability of the treatment effect for the duration of therapy used in the trial. The clinical experts consulted as part of this CADTH Common Drug Review (CDR), the observations made by Health Canada and the US Food and Drug Administration, and the published literature noted that, in clinical practice, some patients may be treated for longer periods than is currently approved. The clinical and economic implications of treating patients with letermovir for longer than the Health Canada–approved duration are unknown.

Background:

Letermovir is an inhibitor of CMV DNA terminase complex belonging to a new antiviral class of quinazolines and has a Health Canada–approved indication for the prophylaxis of CMV infection in adult CMV-seropositive recipients (R+) of an allogeneic HSCT. Letermovir is available as 240 mg or 480 mg oral tablets and as 240 mg per vial or 480 mg per vial solutions for intravenous injection (20 mg per mL). The dosage recommended by Health Canada is 480 mg administered orally or intravenously (240 mg when co-administered with cyclosporine) once daily and should be started after HSCT (may be started on the day of transplant and no later than 28 days post-transplant) through 100 days post-transplant.

Summary of CDEC Considerations:

The committee considered the following information prepared by CDR: a systematic review of RCTs of letermovir and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from clinical experts with experience treating patients undergoing HSCT, and patient group–submitted information about outcomes and issues important to patients.

Patient Input Information

Two patient groups, Lymphoma Canada and Myeloma Canada, responded in a joint submission to the CDR call for patient input. Patient perspectives were obtained from an online survey developed jointly by the two patient groups. The focus of the survey was to understand the impact of HSCT, and the theoretical impact of preventing complications associated with HSCT on patients and their quality of life. No questions specific to CMV infection or its treatment or prevention options were included in the survey. The following is a summary of key input from the perspective of the patient groups:

- Hospitalization throughout the HSCT process has a significant impact on patients (e.g., ability to work). The limited number HSCT treatment centres in Canada forces many patients to travel and be away from home for long periods.
- Patient groups indicated concerns with GVHD and the adverse events associated with the medications used to manage GVHD (e.g., bloating, immune system weakness, extreme fatigue) as well as bacterial, viral, and fungal infections.
- Patients assumed that reducing CMV infection will reduce both GVHD and infections, and result in improved transplant outcomes.
- According to the patient groups, when evaluating any potential new treatments, a patient's quality of life (both during and after transplant) is imperative.
- Overall, cost and accessibility of treatments and monitoring were most important to patients.

Clinical Trials

The CDR systematic review included one phase III double-blind, placebo-controlled, multi-centre, multinational, superiority RCT. Study P001 (N = 570) 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. Patients were randomized in a 2:1 ratio of letermovir administered orally or intravenously at a dosage of 480 mg once daily (240 mg when co-administered with cyclosporine) or matching placebo. Patients could receive treatment up to 14 weeks post-transplant and were followed up to week 24 post-transplant for the primary and secondary end points. Data collection continued to week 48 post-transplant for the evaluation of exploratory outcomes. Patients were monitored for CMV viremia weekly for the first 14 weeks post-transplant followed by biweekly monitoring thereafter through week 24 post-transplant and every other month thereafter through week 48 post-transplant, given the reduced risk of CMV infection.

Limitations associated with the trial include no adjustments for multiple statistical testing other than the primary analysis of the primary efficacy end point, uncertainty regarding the durability of the treatment effect, and patient outcomes beyond 48 weeks post-transplant. Limitations also included the lack of comparative evidence versus a pre-emptive therapy (PET) treatment strategy where PET is initiated at viral loads that are reflective of what would be seen in clinical practice (i.e., viral load greater than and equal to 1,000 copies per mL in patients not receiving primary prophylaxis and depending on patient risk factors).

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- the incidence of clinically significant CMV infection through week 24 post-transplant (defined as initiation of PET based on documented viremia [viral load greater than 150 copies per mL] and the clinical condition of the patient and/or CMV disease)
- the proportion of patients with clinically significant CMV infection through week 14 post-transplant
- the time to onset of clinically significant CMV infection through week 24 post-transplant
- the proportion of patients with CMV disease through week 14 post-transplant and week 24 post-transplant
- the proportions of patients with initiation of PET for documented CMV viremia through week 14 post-transplant and week 24 post-transplant
- the time to initiation of PET for documented CMV viremia through week 24 post-transplant
- all-cause mortality defined as patients who died for any reason while in the study, CMV-related mortality defined as death due to any reason in patients with clinically significant CMV infection and non-relapse mortality defined as death due to any reason other than the primary condition for which a HSCT was performed.
- adverse events (AEs), serious adverse events, withdrawals due to adverse events, and notable harms (cardiac disorders and gastrointestinal disorders).

The primary analysis of the primary outcome in Study P001 was the incidence of clinically significant CMV infection through week 24 post-transplant using the non-completers and missing data method to impute missing data. Analyses other than the primary analysis of the primary end point were not adjusted for multiple statistical testing.

Efficacy

All efficacy outcomes were analyzed in the full analysis set defined as all randomized patients who received at least one dose of study medication and had no detectable CMV viral DNA on day 1, when study medication was initiated.

Compared with placebo, 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). The stratum-adjusted mean difference was −23.5% (95% CI, −32.5 to −14.6), *P* being less than 0.0001 in favour of letermovir. The primary end point of clinically significant CMV infection was primarily driven by initiation of PET and the event rates for CMV end-organ disease were uncommon. The stratum-adjusted mean difference was −30.6% (95%

CI, −40.2 to −21.0), *P* being less than 0.0001, and −0.4% (95% CI, −4.0 to 3.2), *P* being equal to 0.4056 based on non-imputed methods (observed data only). Furthermore, results of the sensitivity analyses and subgroup analyses were generally consistent with the primary analysis.

Clinically significant CMV infection through week 14 post-transplant (stratum-adjusted mean difference) was −31.3% (95% CI, −39.9 to −22.6), *P* being less than 0.0001. The initiation of PET and CMV end-organ disease were also evaluated as secondary end points using imputed methods through week 14 and week 24 post-transplant. The stratum-adjusted mean differences were −31.0% (95% CI, −39.6 to −22.4), *P* being less than 0.0001, and −3.4% (95% CI, −10.0 to 3.3), *P* being equal to 0.1622, through week 14 post-transplant and −23.3% (95% CI, −32.3 to −14.3), *P* being less than 0.0001, and −6.1% (95% CI, −14.4 to 2.2), *P* being equal to 0.0748, through week 24 post-transplant, respectively.

The clinically significant CMV infection Kaplan–Meier (KM) event rates in the letermovir and placebo groups were 6.8% and 41.3% through week 14 post-transplant compared with 18.9% and 44.3% through week 24 post-transplant, respectively. The overall initiation of PET based on documented viremia KM event rates at week 24 post-transplant were 17.2% and 42.4% in the letermovir and placebo groups, respectively. The KM event rates of CMV end-organ disease (the other component of clinically significant CMV) were 1.8% and 2.1% in the letermovir and placebo groups, respectively. Overall, 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 (all-cause mortality of 5.2%, 9.8% and 18.8% compared with 7.1%, 15.9% and 23.5%; CMV-related mortality of 0.3%, 0.9% and 2.8% compared with 1.8%, 8.2% and 13.5%; non-relapse related mortality of 4.0%, 6.5% and 12.0% compared with 5.3%, 10.6% and 15.9% in the letermovir and placebo groups, respectively).

Harms (Safety and Tolerability)

All safety outcomes were analyzed in the all-patients-as-treated set, defined as all randomized patients who received at least one dose of study medication.

Through week 14, week 24, and week 48 post-transplant, a similar proportion of patients in the letermovir group experienced AEs and serious adverse events compared with the placebo group. For AEs, the proportions were 97.9% and 100%, 98.1% and 100%, and 98.4% and 100%, respectively, while for serious adverse events, the proportions were 4.2% and 46.9%, 51.7% and 56.8%, and 54.2% and 59.9%, respectively. A greater frequency of treatment withdrawal due to AEs was reported in the placebo group compared with the letermovir group (51.0% and 19.3%, respectively).

A higher percentage of patients experienced cardiac disorders through week 14 post-transplant in the letermovir group compared with the placebo group (12.6% and 6.3%, respectively) in Study P001. The most common reasons for cardiac disorders were atrial fibrillation (3.5% and 1.0%), sinus tachycardia (1.1% and 1.6%), and tachycardia (4.0% and 2.1%), respectively. The differences between the two groups through week 24 and week 48 post-transplant were 13.7% versus 9.9% and 14.2% versus 10.4% in the letermovir and placebo groups, respectively. The most common cardiac disorders through week 48 post-transplant in the letermovir and placebo groups were atrial fibrillation (3.5% and 1.0%), sinus tachycardia (1.1% and 2.6%), and tachycardia (4.8% and 2.6%), respectively.

A total of 74.8% and 73.4%, respectively, experienced gastrointestinal disorders through week 48 post-transplant. The most common gastrointestinal disorders through week 48 post-transplant in the letermovir and placebo groups were abdominal pain (13.1% and 9.9%), diarrhea (29.5% and 28.6%), nausea (28.7% and 27.6%), and vomiting (21.4% and 18.2%), respectively.

In general, there were more deaths in the placebo group through week 24 and week 48 post-transplant compared with the letermovir group (16.4% compared with 19.8%, and 21.7% compared with 24.5% in the letermovir and placebo groups, respectively). By contrast, there were more deaths in the letermovir group through week 14 post-transplant compared with the placebo group (10.2% and 8.9% in the letermovir and placebo groups, respectively). The most frequently reported reasons for death through week 14 post-transplant (letermovir versus placebo) were GVHD (1.3% versus 1.6%), recurrent acute myeloid leukemia (1.9% versus 1.6%), septic shock (0.8% versus 1.6%), and sepsis (0.8% versus 0.5%), respectively. However, investigators did not consider any of the deaths to be related to study treatment.

Cost and Cost-Effectiveness

Letermovir can be administered orally or intravenously at a dosage of 480 mg daily (240 mg if co-administered with cyclosporine). Letermovir should be started within 28 days of HSCT for up to 100 days post-HSCT. At the manufacturer's submitted price ($251.28 for the oral formulations and the 240 mg intravenous vial, $493.78 for the 480 mg intravenous vial), the average cost per treatment, assuming a treatment course of 100 days, ranges from $25,128 to $49,378.

The manufacturer submitted a cost-utility analysis comparing letermovir as the prophylaxis of CMV infection — taken alongside usual care, in adults CMV-seropositive HSCT recipients — with usual care alone. Usual care consisted of weekly CMV viral load monitoring and initiation of antiviral PET with ganciclovir and/or valganciclovir when CMV viral load was documented greater than 150 copies per mL to 300 copies per mL. The model consisted of a decision-tree that considered three distinct periods: (i) 14 weeks post-transplant (i.e., at the end of the treatment period), (ii) 24 weeks post-transplant, (iii) lifetime. Study P001 was used to inform the 14 week and 24 week model inputs (i.e., initiation of PET, CMV disease, CMV-related hospitalization, opportunistic infections, GVHD, and all-cause mortality). Due to lack of evidence beyond Study P001 duration, the manufacturer estimated long-term survival for patients alive at week 24 by applying an adjusted relative risk of death from a global registry (two to 15 years post-transplant) to age-specific Canadian general population mortality rates. The perspective of the analysis was that of the Canadian public health care system, with costs and benefits discounted at an annual rate of 1.5%. In their probabilistic base case, the manufacturer estimated that the addition of letermovir to usual care compared with usual care alone would result in an ICUR of $27,990 per QALY gained.

CADTH identified a number of limitations with the manufacturer's submitted economic model:

- There was considerable uncertainty around the mortality benefit of letermovir. The manufacturer's results are contingent on the assumption that the benefit in mortality observed with letermovir at week 24 in Study P001 was preserved over a lifetime. Long-term mortality was furthermore underestimated by using survival data in patients that were still alive and disease-free at year 2, as this approach did not account for those who either died or relapsed between week 24 and year 2 post-transplant.
- The manufacturer assumed no cost difference between letermovir and usual care beyond the first year, which potentially underestimates the long-term transplant-related costs in survivors.
- Treatment duration is uncertain and will likely vary. The model structure limited CDR's ability to test the impact of alternative treatment durations.
- Treatment-specific utilities were applied in the first year post-transplant. CDR was unable to test health state–related utilities due to the structure of the model.
- The cost of PET was overestimated, favouring letermovir.

CDR reanalysis adjusted for some of the identified limitations (e.g., a more representative data set for long-term mortality, revised cost of PET) and this resulted in an ICUR for letermovir with usual care of $51,052 per QALY gained compared with usual care alone. The economic results were sensitive to assumptions surrounding long-term mortality, with findings on the cost-effectiveness of letermovir ranging from an ICUR of less than $20,000 per QALY to being dominated (i.e., more costly, less effective).

CDEC Members:

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

May 16, 2018 Meeting

Regrets:

None

Conflicts of Interest:

None