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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

LETERMOVIR (PREVYMIS)

(Merck Canada Inc.)

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

Service Line:	CADTH Common Drug Review
Version:	Final Pharmacoeconomic Review Report (With Redactions)
Publication Date:	July 2018
Report Length:	42 Pages

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Table of Contents

Tables

Figures

CADTH

Abbreviations

CDR	CADTH Common Drug Review
CI	confidence interval
CMV	cytomegalovirus
GVHD	graft-versus-host disease
HSCT	hematopoietic stem cell transplant
ICUR	incremental cost-utility ratio
IV	intravenous
PET	pre-emptive therapy
PP	per-protocol
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RR	relative risk
SE	standard error

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Letermovir (Prevymis)
Study Question	In comparison to usual care, what is the incremental cost-effectiveness of letermovir for the prevention of clinically significant CMV infection in adult CMV-seropositive recipients of an allogeneic HSCT?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult CMV-seropositive HSCT recipients
Treatment	Letermovir of 480 mg per day administered orally or intravenously (240 mg per day when co-administered with cyclosporine A) for 100 days, taken with usual care
Outcomes	Life-years QALYs
Comparator(s)	Usual care consisting of weekly CMV viral load monitoring with initiation of antiviral PET (i.e., ganciclovir and valganciclovir), when appropriate, or treatment of CMV disease
Perspective	Canadian public health care payer
Time Horizon	Lifetime (28 years for patients with mean baseline age of 50.8 years)
Results for Base Case	ICUR = $27,990 per QALY
Key Limitations	• There was considerable uncertainty around the mortality benefit of letermovir. The results are contingent on assuming that the difference in mortality event rate at week 24, as reported in the phase III RCT, is preserved between patients receiving letermovir with usual care compared with usual care alone over a lifetime. Long-term mortality was severely underestimated given the approach used. In both the letermovir with usual care and usual care alone strategies, the life expectancy of patients alive at 24 weeks was extrapolated from a registry of post-transplant patients that selectively incorporated survival data at 2 years to 15 years post-transplant. The approach taken ignored the fact that the publication reported only on the conditional survival among patients who, at year 2 post-transplant, remained alive and disease-free (i.e., approximately 50% of the original cohort); thus, not accounting for those who had either died or relapsed in the initial 2 years post-transplant. • The manufacturer assumed no cost difference between letermovir and usual care beyond the first year, which underestimates the long-term costs associated with letermovir. • Although the manufacturer assumed treatment would be offered only during the first 100 days post-transplant, the treatment duration is uncertain. Clinical experts consulted as part of this CDR noted that it is expected that, in clinical practice, some patients will be treated for longer periods than is currently approved. Similarly, the published literature includes comments that letermovir prophylaxis may be offered for a shorter duration than 100 days. CDR was unable to test the impact of alternative treatment durations due to restrictions in the model's structure. • Treatment-specific utilities were applied in the first year post-transplant, which deviates from best practice for economic evaluations. CDR was unable to test the approaches whereby utilities were elicited due to inflexibility in the manufacturer's model. • The cost of PET was overestimated, favouring letermovir.
CDR Estimate(s)	• In CDR's base-case analysis, long-term mortality rates (> 1 year post-transplant) were calibrated to the reported mortality rates from a large multinational registry and the costs for PET were revised to mirror more reflective Canadian practice. Based on these changes, the addition of letermovir as a prophylaxis alongside usual care in adult CMV-seropositive HSCT recipients resulted in an ICUR of $51,052 per QALY gained, compared

	with usual care alone. A price reduction of 0.1% would be required for the ICUR to be reduced to $50,000 per QALY. • Scenario analyses conducted by CDR highlight the sensitivity of the model to different assumptions on long-term mortality, resulting in a range of ICURs. In the most conservative scenario whereby survival with usual care alone was greater than letermovir taken with usual care (survival difference at week 24: 3%), letermovir was more costly and less effective (i.e., dominated). The least conservative scenario that assumed the largest treatment survival difference (survival difference at week 24: 19% greater on letermovir with usual care compared with usual care alone) resulted in an ICUR of $19,339 per QALY.

CDR = CADTH Common Drug Review; CMV = cytomegalovirus; HSCT = hematopoietic stem cell transplant; ICUR = incremental cost-utility ratio; PET = pre-emptive therapy; QALY = quality-adjusted life-year; RCT = randomized controlled trial.

Drug	Letermovir (Prevymis)
Indication	For the prophylaxis of cytomegalovirus infection in adult cytomegalovirus-seropositive recipients of an allogeneic hematopoietic stem cell transplant
Reimbursement Request	As per indication
Dosage Form(s)	Intravenous infusion: 240 mg and 480 mg per vial Oral: 240 mg and 480 mg tablets
NOC Date	November 1, 2017
Manufacturer	Merck Canada Inc.

Executive Summary

Background

Letermovir is an antiviral agent that can be administered orally or intravenously at a dosage of 480 mg daily (or 240 mg daily if co-administered with cyclosporine A) in patients undergoing an allogeneic hematopoietic stem cell transplant (HSCT) as prophylaxis of cytomegalovirus (CMV) infection.[1] The recommended treatment regimen, as per the Health Canada–approved product monograph, is initiation of letermovir on the day of HSCT or up to 28 days post-transplant and continued through 100 days post-HSCT.[1] At the manufacturer's submitted price ($251.28 for the oral formulations and the 240 mg intravenous [IV] vial, $493.78 for the 480 mg IV vial),[2] the average daily drug cost ranges from $251.28 to $493.78. The average cost per treatment, assuming a treatment course of 100 days, ranges from $25,128 to $49,378 per patient.

The manufacturer submitted a cost-utility analysis comparing letermovir as prophylaxis of CMV infection, taken alongside usual care, in adult (50.8 years old) CMV-seropositive HSCT recipients compared with usual care alone.[2] Usual care consisted of weekly CMV viral load monitoring and initiation of antiviral pre-emptive therapy (PET) with ganciclovir and/or valganciclovir when CMV viral load was documented greater than 150 copies/mL to 300 copies/mL or treatment for CMV-related diseases.[2] The analysis was undertaken from the perspective of the Canadian health care payer. The model structure consisted of a decision-tree that considered three distinct periods: (i) the end of the treatment period (i.e., 14 weeks post-transplant), (ii) 24 weeks post-transplant, and (iii) lifetime.[2] Patients began in a baseline health state of allogeneic HSCT and, at week 14, the model evaluated mortality. At week 24, the model assessed whether complications had developed or patient management was changed due to CMV reactivation. These factors included the initiation of PET, CMV disease, CMV-related hospitalization, opportunistic infection, graft-versus-host disease, and all-cause mortality.[2] Treatment effects at week 14 and week 24 reflected the results of a randomized placebo-controlled phase III trial, Study P001.[3] Due to a lack of long-term information on the comparative efficacy of letermovir with usual care compared with usual care alone, the manufacturer estimated long-term survival of those who remained alive at week 24 by applying an adjusted relative risk of death reported from a global registry (year 2 to year 15 post-transplant) onto age-specific Canadian general population mortality rates.[4] It was assumed that post-transplant costs after the first year would be negligible and only

future benefits were discounted at 1.5% per annum.[2] Treatment-specific utilities were applied only during the first year post-transplant and, thereafter, a utility for post-transplant survivors was applied.[2] Resource use and costs were collected from Canadian cost databases[5,6] and published literature.[7]

In their probabilistic base case, the manufacturer estimated that the addition of letermovir to usual care compared with usual care alone would produce an additional 0.517 quality-adjusted life-year (QALY) for an additional $14,473 per person treated, resulting in an incremental cost per QALY gained of 27,990.[2]

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified several key limitations with the manufacturer's submitted model.

Firstly, there was great uncertainty associated with the estimated long-term effects of treatment on mortality. Mortality was based on an exploratory outcome within the randomized controlled trial.[3] Although all-cause mortality in the trial was assessed at both week 24 and week 48 post-transplant,[3,8] no justification was provided about why the less conservative estimate at 24 weeks was appropriate to be incorporated into the model. Life expectancy was extrapolated in patients who remained alive at 24 weeks post-transplant. The approach taken assumed that the relative difference in mortality event rate at 24 weeks between letermovir with usual care and usual care alone remained constant over the lifetime horizon.[2] Life expectancy was calculated by adjusting baseline Canadian general mortality rates with the increased relative risk of death for underlying diseases in post-transplant patients. The relative risk was taken from a publication that reported late mortality (i.e., two years to 15 years post-transplant) of those who were alive and disease-free two years post-transplant compared with an age-, gender-, and nationality-matched non-transplant population.[9] In this study, data on the transplant population came from a large transplant patient registry. However, the manufacturer's approach to extrapolate life expectancy ignored the fact that this paper reported on the conditional survival in patients who were disease-free and alive at two years post-transplant (i.e., approximately 50% of the original cohort).[9] By using conditional mortality data, the manufacturer's approach underestimated death between week 24 and year 2 post-transplant in both treatment arms. In comparing the model's mortality predictions for the usual care arm to the results reported in the registry, the manufacturer's approach was found to greatly overestimate survival. This is important given that the model was sensitive to inputs that impacted survival estimates and the age of the patient cohort.[2] Secondly, although the manufacturer captured the utility benefit associated with reduced mortality in patients receiving letermovir with usual care, they assumed post-transplant survivors would incur no treatment-related or condition-related costs beyond the first year. This assumption would underestimate long-term costs in both strategies, but would favour letermovir to a greater extent given its mortality benefits compared with usual care only.

Thirdly, variation in treatment duration (e.g., due to protocol-allowed lag time, treatment discontinuation, or treatment extension beyond 100 days post-transplant) did not directly impact the probability of CMV-related health outcomes (e.g., CMV reactivation, CMV-related complications, or death), given the model structure. Although the manufacturer assumed treatment would be offered only during the first 100 days post-transplant, the treatment duration is uncertain. Clinical experts consulted as part of this CDR alongside observations from Health Canada, FDA, and the published literature noted that, in clinical practice, some

patients will be treated for longer periods than is currently approved.[10-12] Similarly, the published literature includes comments that letermovir prophylaxis may be offered for a shorter duration than 100 days. This could not be adequately assessed in the economic analysis.

In addition, treatment-specific utilities values were applied rather than utilities based on CMV-related health outcomes. Therefore, any changes to the probability of CMV-related health outcomes would not have a direct impact on QALYs. Lastly, the calculation of PET costs was not clearly described and could not be reproduced. The clinical experts consulted as part of CDR noted issues with the dosing schedule assumed for PET, as this was not consistent with current Canadian practice.[4] Furthermore, the daily cost of treatment with ganciclovir was overestimated by sevenfold.

In light of these limitations, CADTH attempted to address the limitations by conducting a reanalysis that adjusted mortality to reflect the rates reported within the large patient registry over a more comprehensive time period, and revised the cost estimates to reflect Canadian practice. This resulted in an incremental cost-utility ratio (ICUR) of $51,052 per QALY. Scenario analyses that considered different assumptions surrounding the potential mortality benefit with letermovir produced a wide range of ICUR values reflecting the high uncertainty within the manufacturer's model regarding assumptions on the relative long-term mortality benefit. For example, a scenario that selected the trial-reported 95% upper bounds of mortality for letermovir with usual care and the 95% lower bounds of mortality for usual care only (i.e., survival difference at week 24 was 3% for usual care compared with letermovir with usual care) resulted in letermovir being dominated (i.e., more expensive, less effective). The scenario using the largest survival difference within the trial (i.e., 95% lower bounds of mortality for letermovir with usual care and 95% upper bounds of mortality) resulted in an ICUR of $19,339 per QALY. Of note, the probability of death at 24 weeks was based on the P001 trial in which mortality was an exploratory outcome across all time points evaluated within the trial.

Conclusions

In adults who are CMV-seropositive recipients of an allogeneic HSCT, the CDR base-case reanalyses estimated an ICUR of $51,052 per QALY for letermovir with usual care compared with usual care alone. This analysis is based on the assumption that the difference in mortality event rate in patients receiving letermovir with usual care compared with usual care alone observed at week 24 in the phase III randomized controlled trial is preserved over a lifetime. A price reduction of 0.1% for letermovir would be required for the ICUR to fall below $50,000 per QALY.

The difference in incremental costs was largely driven by the cost of letermovir while the difference in incremental QALY was largely driven by the predicted mortality benefit between letermovir compared with usual care. Significant uncertainty exists with respect to the likely ICUR for letermovir, given the clinical uncertainty with regards to the long-term mortality impacts of letermovir taken alongside usual care compared with usual care alone.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis comparing letermovir with usual care with usual care alone in adult cytomegalovirus (CMV)-seropositive recipients of an allogeneic hematopoietic stem cell transplant (HSCT).[2] Usual care was defined as weekly CMV viral load monitoring with initiation of antiviral pre-emptive therapy (PET) (i.e., ganciclovir and valganciclovir) when CMV viral load exceeded 150 copies/mL to 300 copies/mL and/or treatment of CMV disease.[2] The perspective of the analysis was that of the Canadian public health care payer. The patient population modelled had similar baseline characteristics to patients enrolled in Study P001, a phase III placebo-controlled randomized controlled trial (RCT) with an average age of 50.8 years old.[3] A lifetime time horizon (28 years) was taken in which clinical outcomes — quality-adjusted life-years (QALYs) and life-years — were discounted at 1.5% per annum.[2]

The model estimated the economic consequences of CMV-related events in adult CMV-seropositive recipients of an HSCT following 100 days prophylaxis with letermovir with usual care compared with usual care alone. The model structure was a decision-tree with three distinct periods: (i) 14 weeks post-transplant (coinciding with the end of the Health Canada–indicated treatment of letermovir), (ii) 24 weeks post-transplant, and (iii) lifetime.[2] All patients began as CMV-seropositive allogeneic HSCT recipients and received usual care. At week 14 (i.e., end of treatment period), the model considered the proportion of patients who remained alive. At week 24, the model considered the proportion of patients who would experience complications or changes in patient management due to CMV reactivation such as the initiation of PET for clinically significant CMV reactivation, CMV disease, CMV-related hospitalization, opportunistic infection, graft-versus-host disease (GVHD) and death (from all causes).[2] The clinical findings from Study P001 were used to estimate the treatment effects for letermovir with usual care and for usual care alone following the first 24 weeks post-transplant.[3] Life expectancy was extrapolated for patients on letermovir with usual care and for patients on usual care alone to extend the model to a lifetime time horizon.[2] Given the lack of long-term comparative efficacy data, the manufacturer took the same approach to estimated life expectancy in both treatment arms. The life expectancy of patients who remained alive at week 24 post-transplant was estimated from age-specific Canadian general population mortality rates,[13] adjusted by an increased relative risk (RR) of death that was derived from a publication that compared mortality rates of transplant patients against mortality rates of a general US population.[9] That study specifically reported on long-term mortality and late deaths (i.e., between two and 15 years post-transplant) based on data from a multinational registry from the Center for International Blood and Marrow Transplant Research. As this publication did not report a RR of death in the first year post-transplant, the manufacturer assumed that the RR of death in the first year post-transplant would be identical to the second year post-transplant values (i.e., RR = 10.36).[2,9]

Treatment-specific utilities were applied during the first year post-transplant only and were derived from the trial as the reported change in utilities from baseline to week 24.[3] Beyond the first year, utilities weight for survivors was assumed to be a constant value of 0.76 regardless of treatment.[14]

The model included drug cost for letermovir and PET, monitoring costs, and medical costs to manage CMV-related events. The prices for letermovir were obtained from the manufacturer.[2] Total treatment costs were calculated based on assuming a mean duration of treatment of 70 days, similar to the treatment duration observed in the P001 trial.[3] Costs were further weighted such that [redacted]% of patients were assumed to be on the oral formulation while the remaining [redacted]% of patients would begin on the intravenous (IV) dosage for the first nine days ([redacted]% receiving concomitant cyclosporine A that would result in lowering the dose of letermovir to 240 mg) before switching to the oral formulation (240 mg) for the remaining 61 days of prophylaxis treatment.[2] No cost of prophylaxis was applied to the usual care strategy.[2] The cost of usual care included weekly monitoring, with the frequency of disease monitoring assumed identical for both arms of the model. PET consisted of ganciclovir 5 mg/kg daily for 29.2 inpatient days and valganciclovir 900 mg daily for 30.1 outpatient days.[2] Other medical costs for CMV-related events were calculated based on costs from Canada databases and adjusted to account for resource use based on either post hoc analyses of Study P001[15] or from American inpatient claims data.[7] The exception was CMV disease, which was set to zero to prevent double-counting with CMV infection. The manufacturer further assumed no difference in PET-related adverse events and that, beyond the first-year post-transplant, survivors would not incur any further treatment-related or condition-related costs.[2]

Manufacturer's Base Case

The manufacturer's deterministic base case and associated probabilistic analysis were reported for a cohort of 100 patients. In accordance with CADTH's *Guidelines for Economic Evaluation of Health Technologies*, the CADTH Common Drug Review (CDR) adjusted the calculations to report the results per patient.[16] According to the manufacturer's base case, the use of letermovir with usual care for CMV prophylaxis will result in incremental costs of $14,473 and incremental QALYs of 0.52 per patient compared with usual care alone over a 28-year time horizon.[2] Results from the manufacturer's probabilistic base case are shown in Table 2 and highlight that the incremental cost-effectiveness of letermovir with usual care compared with usual care alone is $27,990 per additional QALY gained. Based on the manufacturer's analysis, letermovir plus usual care had a 78.9% probability of being the most likely cost-effective option at a cost-effectiveness threshold of $50,000 per QALY.[2]

Table 2: Summary of Probabilistic Results of the Manufacturer's Base Case (Per Patient)

	Usual Care	Letermovir, Taken with Usual Care	Difference (Letermovir Taken with Usual Care – Usual Care)
Total Costs	$14,062	$28,535	$14,473
Total QALYs	7.36	7.88	0.52
ICUR ($/QALYs)			$27,990

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Source: Manufacturer pharmacoeconomic submission.[2]

Summary of Manufacturer's Sensitivity Analyses

The manufacturer performed a series of one-way deterministic sensitivity analyses to determine the impact of individual model parameter inputs on the base case results (e.g., discounting, patient age, treatment effect, utility values, costs). The model was most

sensitive to inputs that reduced the magnitude of the mortality benefit between the two treatment strategies, such as the probability of all-cause mortality at 24 weeks and the mean age of the patient population.[2] Specifically, by reducing the mortality benefit between treatment strategies (such as narrowing the relative treatment difference in survival or increasing patient's age), the model produced a larger incremental cost-utility ratio (ICUR). For instance, by assuming identical mortality rates between treatments (i.e., setting all-cause mortality for the usual care arm to its lower bound of the 95% confidence interval (CI)), the ICUR was above $400,000 per QALY. On the other hand, setting the probability of all-cause mortality at 24 weeks in the letermovir arm to the lower bound of the 95% CI (i.e., 6.8%) generated an ICUR of $17,737 per QALY.[2] Similarly, when the mean age of patients was set to 78 years old, the resulting ICUR was slightly below $200,000 per QALY.[2] All other parameters tested generated ICUR lower than $50,000 per QALY.[2]

Although the manufacturer's pharmacoeconomic report mentioned a sensitivity analysis performed using the 48-week phase III RCT outcomes, no results from this analysis were reported and no other scenario analysis was performed.

Limitations of Manufacturer's Submission

CDR identified the following key limitations with the manufacturer's model.

1. **Modelling long-term treatment benefits:** There was substantial uncertainty around the approach taken to modelling the long-term effects of treatment. In the clinical trial, mortality was an exploratory end point assessed at week 14, week 24, and week 48 post-transplant. The manufacturer selected mortality at 24 weeks to project long-term survival. No justification was provided behind the selection of week 24 mortality data and the difference in mortality at 24 weeks was numerically larger (i.e., less conservative) than all other time periods assessed. For example, the mean difference for week 14 was 1.9% and for week 48, was 4.6%, but for week 24, the mean difference was greater than both periods at 5.7%.[2] As the clinical review noted, the analysis at week 24 excluded 76 subjects who withdrew prematurely from the trial at week 24. Although discontinuation was balanced between study arms, FDA requested reanalyses that included the vital statuses of 58 of the 76 patients who had discontinued, resulting in a higher mortality rate for both treatment arms (i.e., probability of death at 24 weeks: 12.1% for letermovir with usual care versus 17.2% for usual care alone).[17,18]

   The life expectancy of those still alive at 24 weeks was extrapolated. As the same methods were used to estimate life expectancy in both the letermovir with usual care arm and the usual care alone arm, this meant that the relative treatment difference in mortality event rate at 24 weeks remained constant over a lifetime. Discussions with the clinical experts consulted as part of this CDR and comparisons made to published literature[9,19,20] showed that the method and assumptions taken to determine life expectancy in transplant patients underestimated overall mortality. Specifically, life expectancy was calculated by adjusting Canadian life tables[13] with the reported increased RR of death for underlying diseases in post-transplant patients compared with a general population.[2] The RR came from a publication that reported late mortality (i.e., two years to 15 years post-transplant) of transplant patients who remained alive and disease-free beyond the first two years of their transplant. The data for this publication came from a large multinational transplant patient registry maintained by the Center for International Blood and Marrow Transplant Research and was compared

with an age-, gender-, and nationality-matched non-transplant population.[9] The manufacturer assumed that the RR of death in the first year post-transplant was identical to the RR of death in the second year.[2] This assumption negated the fact that this international registry publication reported specifically on the long-term survival of patients who were alive and disease-free at year 2 (i.e., approximately 50% of the original cohort), thus ignoring those who had either died or relapsed in the initial two years post-transplant.[9] The manufacturer's approach to modelling long-term survival resulted in much higher overall survival rates than has been reported in the literature for such patients.[19] It is unclear why the manufacturer's model used only the mortality data from year 2 post-transplant onward and did not consider the higher early mortality rates (i.e., < two years post-transplant). The assumptions made by the manufacturer were optimistic as they resulted in an overall mortality of 15% and 20% by the second year for the letermovir with usual care arm and the usual care alone arm, respectively. Other reports from the same international registry have reported two-year to three-year overall mortality in the range of 40% to 60%.[19,20] In summary, the approach taken and assumptions made by the manufacturer were overly optimistic in estimating life expectancy in transplant patients who survived 24 weeks.

In the CDR reanalysis, treatment-specific 24-week and 48-week mortality outcomes reported in the P001 trial were incorporated into the model, with the year 1 mortality probability assumed equal to the mortality rates reported at 48 weeks. Furthermore, in the CDR reanalysis, natural history with respect to overall mortality at year 3 post-transplant was calibrated to reflect the observed values from the Center for International Blood and Marrow Transplant Research registry. This approach meant that overall mortality for the usual care only strategy would trend back toward the expected overall mortality reported in the registry while the addition of letermovir to usual care resulted in a decrease in the overall mortality event rate compared with the usual care arm, similar to that which was observed at week 24 in the P001 trial. Several scenario analyses were also conducted that varied the potential long-term mortality benefits of treatment and incorporated the mortality outcomes from the FDA reanalysis.

2. **Not including post-transplant costs beyond the first year**: The manufacturer assumed post-transplant survivors would not incur further medical costs beyond the first year.[2] This assumption is optimistic. The model accounted for the clinical benefits associated with treatment due to improved mortality, but ignored the potential long-term medical costs associated with being a transplant survivor. A study in Sweden reported that, although medical costs are higher during the first year post-transplant, survivors continue to incur medical costs beyond the first year after transplant.[21] As no Canadian data on the long-term medical costs associated with post-HSCT survivors was available, CDR was unable to conduct a reanalysis that incorporated long-term medical costs in transplant survivors. By capturing long-term clinical benefits but not long-term costs, the economic model favoured letermovir, given the effects of treatment on overall mortality.

3. **Uncertainty with the impact of variable treatment durations**: The model lacked flexibility as it could not address the potential impact of variable treatment duration on letermovir. This made validation and evaluation challenging, especially in testing alternative scenarios. Variation in the duration of treatment (i.e., treatment discontinuation, treatment failure) was not linked to treatment efficacy. As a result, the model didn't show how different lengths in the treatment periods could impact the development of CMV-complications.[2] Similarly, overall treatment costs were based on

the average duration of treatment (70 days) observed in the entire letermovir study cohort.[3] Although this is aligned with Study P001, different treatment durations could not be adequately tested in the manufacturer's model — including whether treatment duration adhered to the 100 days recommended in the product monograph,[1] as variation in the length of treatment was not directly linked to differences in the development of health outcomes such as CMV reactivation, CMV-related complications, or death. CDR was unable to adequately assess the impact of a treatment duration longer or shorter than the 70 days that was used in the submitted model. Furthermore, the manufacturer assumed treatment would only be available for the first 100 days post-transplant as per the product monograph;[1] however, the clinical experts consulted as part of this CDR noted that, in clinical practice, some patients may be treated for longer periods (as was observed in the P001 study in which the maximum treatment duration was 113 days).[3] A more appropriate model would have been one that considered the length of treatment and how this impacts treatment costs and the probability of developing CMV-related health outcomes.

4. **Approach to estimate and apply treatment-specific utility values**: As per current Canadian guidelines for the economic evaluation of health care technologies,[16] the use of treatment-specific utilities deviates from best practice as utility weights based on health states are recommended. No justification was provided in support of the use of treatment-specific utilities. This resulted in poor flexibility to model changes in the incidence of CMV-related complications and its impact on QALYs. Changes to the incidence of events such as opportunistic infections, GVHD, and CMV infections would not impact the calculation of QALYs. Furthermore, treatment-specific utilities were derived from the P001 trial as the difference from baseline utility to the utility of those who remained in the study at 24 weeks of the P001 trial.[3] Although the completion rate of the EuroQoL 5-Dimensions (EQ-5D) questionnaire was similar in both arms (62% to 76% of those for whom it was expected, depending on time point), a FDA requested reanalysis on mortality that included those who discontinued from the trial resulted in a higher mortality rate, suggesting that those who discontinued were likely more ill.[17,18] Therefore, if treatment-specific utilities were calculated to account for those who discontinued being in the trial, the expected utility benefit associated with each treatment would be expected to be a lower value. Given the inflexibility with how utilities were coded in the economic model, CDR was unable to address this overall limitation.

5. **Cost of pre-emptive therapy overestimated**: The manufacturer assumed a PET regimen consisting of ganciclovir 5 mg/kg daily for 29 days followed by 900 mg valganciclovir for 30 days.[2] According to the clinical experts consulted by CADTH for this review, this is not consistent with current practice in Canada.[4] Most bone marrow transplant centres in Canada use ganciclovir 5 mg/kg twice daily for 14 days as induction (extending to 21 days if viremia remained present at day 14), followed by ganciclovir 5 mg/kg daily for an additional four weeks. Variability was noted by the clinical experts consulted as part of this CDR. In some Canadian centres, PET may instead consist of valganciclovir 900 mg twice daily for the entire six-week period. As the price of ganciclovir is much more expensive than valganciclovir, the manufacturer's assumption of the drug regimen for PET would have underestimated the overall costs of PET. However, the daily cost of ganciclovir for a 70 kg individual was also found to be overestimated by a factor of seven in the manufacturer's submission (i.e., $307[2] rather than $43). The combination of both issues (i.e., incorrect dosage and regimen and daily costs) resulted in an overestimation of the cost of PET. In the CDR base-case

reanalysis, PET consisted of a six-week regimen with ganciclovir with scenario analyses conducted based on a regimen involving valganciclovir.

See Table 7 for other comments on submission quality.

CADTH Common Drug Review Reanalyses

In light of the identified limitations with the manufacturer's analysis, CADTH undertook a series of additional analyses in order to address the limitations identified. CADTH considered the following revisions to the submitted model to inform the CDR base case.

- Modification of all-cause mortality to be consistent with the reported mortality in this patient population: one-year survival equal to 48-week phase III RCT results, three-year survival as per Teira et al., (51.25%, this was the weighted average of overall survival for underlying disease post-transplant; lymphoma was not presented in the analysis and data from chronic myeloid leukemia was used as a proxy).[19] The survival value at two years (61.79%) was interpolated from the two time points (year 1 and year 3 post-transplant) based on log transformation.
- Modification of PET regimen to better reflect Canadian practice (14-day induction regimen with ganciclovir of 5 mg/kg twice daily followed by a 28-day maintenance regimen with ganciclovir of 5 mg/kg daily).
- Creation of a cohort size of 1.
- Correction of multiple errors on values used for PSA (see Appendix 5 for details).

All values used by CADTH as part of the revised base case are listed in Table 11 of Appendix 5. The results of the CDR base-case reanalysis are reported in Table 3. CDR conducted one-way sensitivity analysis on each of the identified limitations that could be tested in the base case. These one-way sensitivity analyses can be found in Table 12 of Appendix 5.

CADTH further performed the following scenario analyses to address some of the uncertainties previously identified with respect to long-term mortality benefits of letermovir with usual care compared with usual care alone and the potential variability in clinical practice. Further scenario analyses are presented in Table 13 of Appendix 5.

- **Scenario 1**: The smallest difference in mortality at 24 weeks based on P001 trial;[3] i.e., the upper limit of 95% CI for letermovir with usual care (13.6%) and the lower limit of 95% CI for usual care alone (10.2%).
- **Scenario 2**: The largest difference in mortality at 24 weeks based on P001 trial;[3] i.e., the lower limit of 95% CI for letermovir with usual care (6.8%) and the upper limit of 95% CI for usual care alone (21.6%).
- **Scenario 3**: Valganciclovir 900 mg twice daily for six weeks as PET.

Compared with the manufacturer's results, the CDR reanalysis resulted in lower expected costs and QALYs for both letermovir with usual care and usual care alone. CDR's base case resulted in an ICUR of $51,052 per QALY, as opposed to $27,990 per QALY as reported in the manufacturer's base case. Scenario analyses highlight the sensitivity of the model to the estimated survival benefit. When the difference in mortality between treatment was reduced (Scenario 1), the addition of letermovir to usual care was found to be dominated (i.e., more expensive, less effective). On the other hand, the scenario in which the difference in mortality increased (Scenario 2) reduced the ICUR to $19,339 per QALY. Given the variability of PET regimen across Canada, a scenario analysis was conducted in which PET

regimen consisted of valganciclovir 900 mg twice daily. It was found to have little impact on the ICUR ($51,153 per QALY).

Table 3: Results from Selected CADTH Reanalyses

Scenario		Treatments (Difference)	Total Costs	Total QALY	ICUR (per QALY)
Manufacturer's base case		Usual care	$14,062	7.36	
		Letermovir, taken with usual care	$28,535	7.88	
		Incremental	$14,473	0.52	$27,990/QALY
CDR base-case reanalysis		Usual care	$6,757	4.78	
		Letermovir, taken with usual care	$23,088	5.10	
		Incremental	$16,331	0.32	$51,052/QALY
1	Smallest difference in mortality event rate (i.e., upper bounds of 95% CI for letermovir and lower bounds of 95% CI for usual care)	Usual care	$6,769	5.10	
		Letermovir, taken with usual care	$22,924	4.91	
		Incremental	$16,155	−0.19	Dominated
2	Largest difference in mortality event rate (i.e., lower bounds of 95% CI for letermovir and upper bounds of 95% CI for usual care)	Usual care	$6,760	4.45	
		Letermovir, taken with usual care	$22,983	5.29	
		Incremental	$16,223	0.84	$19,339/QALY
3	PET regimen consisting of valganciclovir 900 mg b.i.d.	Usual care	$6,124	4.78	
		Letermovir, taken with usual care	$22,747	5.10	
		Incremental	$16,623	0.33	$51,153/QALY

b.i.d. = twice daily; CDR = CADTH Common Drug Review; CI = confidence interval; ICUR = incremental cost-utility ratio; PET = pre-emptive therapy; QALY = quality-adjusted life-year.

CADTH undertook price reduction analyses on the CDR base-case analysis and manufacturer's base-case analysis. Results of the price reduction scenarios can be found in Table 4. Under the CDR base case, each 10% reduction in price consistently reduced the ICUR between $5,000 and $6,000 per QALY. Using the CDR reanalysis, letermovir would be cost-effective at $50,000 per QALY following a price reduction of 0.1%.

Table 4: CADTH Common Drug Review Reanalysis Price Reduction Scenarios

ICURs of Letermovir with Usual Care vs. Usual Care Alone ($/QALY)		
Price	**Base-case Analysis Submitted by Manufacturer**	**Reanalysis by CDR (Based on CDR Base Case)**
Submitted	$27,990	$51,052
0.1%		$50,241
10%	$26,662	$44,129
20%	$21,028	$38,876
30%	$17,714	$32,979
40%	$14,223	$27,232
50%	$10,820	$22,154

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Issues for Consideration

- In Canada, HSCT is performed in a limited number of hospitals. This may, therefore, require patients to temporarily travel to specialized centres for treatment. As per the clinical experts consulted in this review, patients are monitored by the transplant centre for up to 100 days post-transplant, after which patients return to their own communities and are sent back to their local clinical team. CMV prophylaxis might therefore be an option for patients who do not live near transplant centres.
- CMV testing is required to ensure that patients are suitable for prophylaxis. In fact, treatment estimates in the economic model came from efficacy data of the full analysis set within Study P001. The full analysis set was defined as all randomized patients who received at least one dose of study medication and had no detectable CMV viral DNA on the first day of treatment. CMV levels should also be monitored as per standard practice while the patient receives letermovir.[4]
- According to the clinical experts consulted as part of this review, the threshold whereby PET is initiated due to CMV reactivation is semi-subjective. The threshold depends on patients' risk factors and whether the management of CMV disease is in a pre-emptive or prophylactic setting. In a pre-emptive setting, the threshold at which PET is commonly initiated is when CMV viral load exceeds 1,000 copies per mL in patients at low risk of CMV reactivation. In patients at high risk of CMV reactivation (e.g., donor serostatus, level of immunosuppression), PET may be initiated at lower thresholds.[4] The clinical experts noted that the thresholds adopted in the clinical trials were more conservative (150 copies per mL to 300 copies per mL)[3,8] and more aligned to the initiation of PET in a prophylaxis setting. In clinical practice, a higher threshold may be applied to the usual care arm (as this closely resembles a pre-emptive strategy) to define CMV reactivation that would result in the initiation of PET. However, the clinical experts noted that the probability of initiating PET in the usual care arm of the P001 trial was similar to the probabilities of PET initiation in their respective clinical settings.
- There are several drug-drug interactions with letermovir due to its effects on cytochrome P450. In particular, letermovir increases blood levels of those exposed to cyclosporine A, tacrolimus, and sirolimus, products that are likely to be administered in the target population. Blood levels of people exposed to these products must be monitored and their dosage reduced if necessary, although the manufacturer's model did not capture this. Other drug-drug interactions are expected to be observed as letermovir reaches the market.

Patient Input

Input was received from a joint submission from Lymphoma Canada and Myeloma Canada that reported on common experiences and complications with allogenic stem cell transplant in patients with blood, plasma cell, or lymphoid cancers. Of the 103 patients surveyed, it was unclear who had an allogenic stem cell transplant — and, of those, the proportion who were CMV-seropositive recipients. No information was available on the specific impact of CMV infection on patients or patient expectations about letermovir. Patients noted the burden of leaving their home or communities to receive a transplant. Common complications noted in the patient input were non-specific to CMV reactivation and included infections (e.g., bacterial, viral, or fungal), internal organ problems, graft failure, or rejection. From the patient input received, it was not clear if the concerns raised were specific to patients with CMV infections.

Conclusions

The manufacturer's pharmacoeconomic submission had several key limitations, the most important being the assumption taken on the long-term mortality benefits of letermovir with usual care compared with usual care alone. Based on CDR reanalyses, the addition of letermovir as a prophylaxis alongside usual care in adult CMV-seropositive HSCT recipients resulted in an ICUR of $51,052 per QALY gained when compared with usual care alone, if the difference in mortality event rate observed in the P001 trial at week 24 for letermovir compared with usual care was maintained throughout a lifetime. The difference in incremental costs was largely driven by the cost of letermovir while the difference in incremental QALY was largely driven by the estimated life expectancy of patients. The model was found to be sensitive to any parameters that impacted the calculation to predict life expectancy. Also, it was not possible to adequately evaluate the impact of alternative treatment durations, given the structure of the model. Uncertainty around long-term mortality benefits was tested via scenario analyses and resulted in wide variations from letermovir taken with usual care being dominated to an ICUR of $19,339 per QALY compare to usual care alone.

At the current price, the likelihood that the addition of letermovir to usual care would be cost-effective at a willingness-to-pay threshold of $50,000 per QALY was 51.5% under CDR's base case reanalysis. A price reduction of 0.1% would be required for letermovir to achieve an ICUR lower than $50,000 per QALY.

CADTH notes that the results only apply to patients who are treated in the first 100 days post-transplant. The manufacturer's model was not sufficiently flexible to model patients whose treatment is extended beyond the first 100 days post-transplant.

Appendix 1: Cost Comparison

Clinical experts have deemed the comparators presented in Table 5 to be appropriate. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs; they may be devices or procedures. Costs are manufacturer's list prices, unless otherwise specified. Existing product listing agreements are not reflected in Table 5 and, as such, may not represent the actual costs to public drug plans.

Table 5: CADTH Common Drug Review Cost Comparison Table for Antivirals Against Cytomegalovirus

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Cost per Treatment Course ($)
Letermovir (Prevymis)	240 mg 480 mg	tablet	$251.2800[a]	480 mg per day (or 240 mg per day if administered concomitantly with cyclosporine A) for 100 days post-transplant	$251.28	$25,128 if administered with or without cyclosporine A
	240 mg per vial	IV	$251.2800[a]		$251.28	$25,128 if administered with cyclosporine A
	480 mg per vial	IV	$493.7800[a]		$493.78	$49,378 if administered without cyclosporine A
Other CMV prophylaxis treatments						
Ganciclovir (Cytovene)[c]	500 mg per vial	IV	$43.9340	Induction: 5 mg/kg q.12,h. for 7 to 14 days Maintenance: 5 mg/kg per day for 100 to 120 days	Induction: $87.87[b] Maintenance: $43.93[b]	$5,008.48 to $6,502.23
Valganciclovir (Valcyte and generics)[e]	450 mg	Tablet	$5.8553	900 mg q.d. (as per product monograph) or b.i.d. (as per clinical experts), to be started within 10 days of transplant and continued for 100 days post-transplant	$11.71 to $23.42	$1,171.06 to $2,342.12
	50 mg/mL	Powder for oral solution	$2.6783[d]		$48.21 to $96.41	$4,820.94 to $9,641.88
Pre-emptive therapy regimen						
Ganciclovir (Cytovene)	500 mg per vial	IV	$43.9340	Induction: 5 mg/kg b.i.d. for 14 days Maintenance: 5 mg/kg/day for 4 weeks	Induction: $87.87[b] Maintenance: $43.93[b]	$2,460.30
Valganciclovir (Valcyte and generics)	450 mg	Tablet	$5.8553	900 mg/day for 6 weeks	$11.71	$983.64

b.i.d. = twice daily; CMV = cytomegalovirus; HSCT = hematopoietic stem cell transplant; ICUR = incremental cost-utility ratio; IV = intravenous; PET = pre-emptive therapy; QALY = quality-adjusted life-year; q.12.h = once every 12 hours; q.d. = once daily; RCT = randomized controlled trial.

Note: Formulary list prices (accessed March 2018) unless otherwise indicated; does not include dispensing fees. Recommended dosages from respective product monographs unless otherwise indicated.

[a] Manufacturer submitted price.[2]
[b] Assumes patient weight of 70 kg.
[c] Requires in addition 900 mg per day of valganciclovir from day 100 to day 365, adding $3,103.15 to the cost of the treatment regimen.[4]
[d] Alberta Drug Benefit List (accessed March 2018).[23]
[e] Not specifically indicated for prophylaxis of CMV in HSCT.

Source: Ontario Drug Benefit.[22]

Appendix 2: Summary of Key Outcomes

Table 6: Letermovir With Usual Care Relative To Usual Care Alone — Attractiveness Considering Only Costs, Outcomes, and Quality of Life

Letermovir With Usual Care vs. Usual Care Alone	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (Total)				X		
Drug Treatment Costs Alone					X	
Clinical Outcomes			X[a]			
Quality of Life			X[b]			
Incremental CE Ratio or Net Benefit Calculation	Manufacturer's base case: $27,990 per QALY[2] CDR base case: $51,052 per QALY					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.

[a] There was considerable uncertainty on the long-term benefit of letermovir as mortality was an exploratory end point at all study time points and mortality has not been explored beyond 48 weeks in Study P001.

[b] There was considerable uncertainty on the relative quality of life difference between letermovir with usual care compared with usual care alone. Utilities within the model were treatment-specific and derived from the trial that captured the utility of only those who remained on treatment. Although the trial indicates a difference in the rates of cytomegalovirus-related complications, there was no evidence to indicate to what extent utilities would be weighted differently for specific complications.

Appendix 3: Additional Information

Table 7: Submission Quality

	Good (or Yes)	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments: Reviewer to provide comments if answering "no"	• Several values for the one-way analysis and PSA were not appropriate. They included the following. ○ **Probabilities of PET (i.e., clinically significant CMV infection in the model) and CMV disease at each time point and for each treatment arm:** The lower and upper limits of the 95% CI as well as the appropriate number of events for the alpha and beta parameters should have been used to define the parameter distribution. ○ **Letermovir treatment costs:** Standard deviation for the parameter distribution was set at 10% of the average value. Although none of the publications report variability around the dose administered, within the CSR for Study P001, tables 14.3-1, 12-2, and 12-23 allow variability that could have been used to be estimation (i.e., ranges of treatment duration). ○ **Uncertainty around estimates for long-term mortality:** Uncertainty was not considered in the PSA, even though the 95% CI was available from the data source.[4] ○ **Ganciclovir costs could not be reproduced:** The costs used by the manufacturer were sevenfold greater than costs recalculated by CADTH. • Certain details pertaining to treatment efficacy described in the manufacturer's PE report and accompanying Excel model did not align with the clinical data provided by the manufacturer. Similarly, certain details within the PE report did not align with the accompanying Excel model. For instance: ○ the utility value post-year 1 was 0.82 in the PE report vs. 0.76 in the Excel model ○ there are several discrepancies noted in Table 1, Table A-1, and Table B-1 of the PE report; tables A-1 and B-1 should have been updated to reflect the values that were actually used in the analyses ○ the model figure within the Structure worksheet in the Excel model does not correspond to the structure of the model reported in the PE report.		
Was the material included (the content) sufficient?	X		
Comments: Reviewer to provide comments if answering "poor"	None		
Was the submission well organized and was information easy to locate?	X		
Comments: Reviewer to provide comments if answering "poor"			

CI = confidence interval; CMV = cytomegalovirus; CSR = Clinical Study Report; PE = pharmacoeconomic; PET = pre-emptive therapy; PSA = probabilistic sensitivity analysis.

Table 8: Authors Information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR
☐ Adaptation of global model/Canadian model done by the manufacturer ☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer ☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer ☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document			X
Authors had independent control over the methods and right to publish analysis			X

Appendix 4: Summary of Other Health Technology Assessment Reviews of Drug

Letermovir has not yet been reviewed by the UK's National Institute for Health and Care Excellence, the Scottish Medicine Consortium, the Haute Authorité de Santé, or the Australian Government's Pharmaceutical Benefits Advisory Committee. The National Institute for Health and Care Excellence is currently reviewing letermovir (an invitation to participate in the public consultation was posted on January 8, 2018)[24] and a submission is expected by the Scottish Medicine Consortium (no published date).

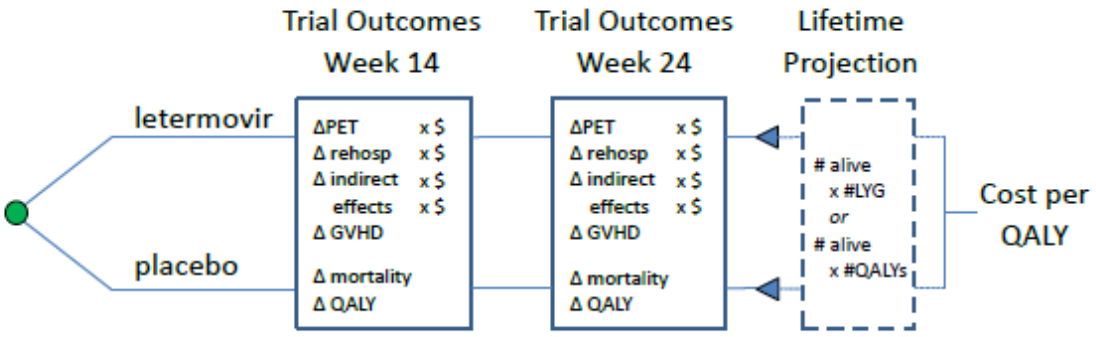
Appendix 5: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer submitted a decision-tree that considered a lifetime horizon (28 years) in a patient cohort with an average age of 50.8 years. Patients included in the model were cytomegalovirus (CMV)-seropositive recipients of an allogeneic hematopoietic stem cell transplant due to various underlying diseases such as acute myelogenous leukemia, myelodysplastic syndrome, non-Hodgkin lymphoma, and acute lymphocytic leukemia.[2] The model structure consisted of a decision-tree consisting of three distinct periods: (i) 14 weeks post-transplant (coinciding with the end of the treatment period), (ii) 24 weeks post-transplant and (iii) lifetime.[2]

All patients entered the model following an allogeneic hematopoietic stem cell transplant and, at 14 weeks — the end of prophylaxis with letermovir as per the product monograph[1] — the proportion of patients remaining alive were considered. At 24 weeks post-transplant, the model considered complications or changes in patient management due to CMV reactivation (i.e., patients initiating pre-emptive therapy for clinically significant CMV reactivation, CMV-related hospitalizations, opportunistic infections, graft-versus-host disease, and mortality). The model could also capture CMV disease and pre-emptive therapy-related adverse events, but these were not included in the manufacturer's base-case analysis (see Table 9 for explanation). Lifetime projections of the cohort were applied to those who remained alive at week 24 to estimate the expected life expectancy of patients. The structure of the model, as presented in the manufacturer's pharmacoeconomic submission, can be found in Figure 1, although this figure does not truly reflect the mechanics of the submitted model.[2]

Figure 1: Manufacturer's Model Structure



GVHD = graft-versus-host disease; LYG = life-year gained; PET = pre-emptive therapy; QALY = quality-adjusted life-year.

Source: Manufacturer pharmacoeconomic submission.[2]

The manufacturer used the findings reported in the P001 trial to inform treatment-specific parameters on complications and changes in patient management due to CMV reactivation and mortality at week 14 and week 24.[3] Life expectancy was extrapolated among patients

who remained alive at week 24 in each respective treatment arm.[2] The same approach was taken to estimate life expectancy in both letermovir with usual care and usual care only arms. The life expectancy of patients who remained alive at week 24 post-transplant was calculated from age-specific Canadian general population mortality rates,[13] adjusted by an increased relative risk (RR) of death that was derived from a publication that compared mortality rates of transplant patients from a multinational registry of the Center for International Blood and Marrow Transplant Research against general US population rates.[9] As the study reported only the increased risk of death from two to 15 years post-transplant, the manufacturer assumed that the RR of death in the first year post-transplant would be identical to second year post-transplant (i.e., RR) of death in transplant patients compared with a general non-transplant population = 10.36).[2]

Table 9: Data Sources

Data Input	Description of Data Source	Comment
Efficacy	Probability of CMV-related complications and changes in patient management due to CMV-related reactivation at 24 weeks post-transplant was taken from the phase III RCT (full analysis set population).[3,8] Efficacy outcomes considered in the model include: • clinically significant CMV infection (defined as 150 copies/mL to 300 copies/mL) • CMV disease • CMV-related rehospitalization • opportunistic infection • GVHD • all-cause mortality (see *Mortality* for further details).	Aspects of the study may have limited the generalizability of the study results to a Canadian setting. Only 1 out of the 67 centres was conducted in Canada.[3] The study further included stringent inclusion and exclusion criteria that could have resulted in a highly enriched population. Furthermore, differences in clinical practice were noted by the clinical experts consulted for this review as the trial included a higher proportion of patients that used non-myeloablative conditioning regimens than would be expected in clinical practice in Canada and used a more conservative threshold to initiate PET. Conventionally, PCR is the preferred test for viremia with positive thresholds for CMV reactivation typically defined at 500 copies/mL to 1,000 copies/mL.[4] In the P001 trial, a lower threshold was selected, i.e., 150 copies/mL to 300 copies/mL.[3] The more conservative threshold used in the trial may have increased the number undergoing PET; however, the bias introduced would have likely been similar in both arms. The full analysis set was defined as all randomized patients who received at least one dose of study medication and had no detectable CMV viral DNA on day 1.[3] The economic model did not incorporate the efficacy data of treatment that was reported at 48 weeks post-transplant within the trial.[8] The probabilities of CMV-related complications were higher at week 48 than week 24 in both arms of the study.[3,8] Furthermore, there was no data on the long-term efficacy beyond 48 weeks post-transplant. Variation in the duration of prophylaxis (due to treatment discontinuation, treatment failure, and treatment extension) was not directly linked to treatment efficacy.
Target Population (Generalizability)	Age at transplant is set at 50.8 years as per the reported average age in P001 trial.[2]	The median age in the Canadian Bone Marrow Transplant Group 2015-2016 annual report was 46.1 years.[25]

Data Input	Description of Data Source	Comment
	In the clinical study, HSCT is performed mainly for AML (37.9%), MDS (15.0%), NHL (13.3%), and ALL (8.8%).[3]	Appropriate. The Canadian Bone Marrow Transplant Group 2015-2016 annual report noted that AML, ALL, CML, MDS, and NHL were the top diseases for which an allogeneic transplant was performed in an 18,000-patient registry.[25]
Utilities	Treatment utility was calculated as the change in baseline utility (EQ-5D) to week 24 in patients who continued in the P001 trial (based on UK EQ-5D tariffs).[2] Letermovir arm: 0.107 (range: 0.108 to 0.164) Usual care arm: 0.025 (range: 0.040 to 0.084)	It is recommended that health state utilities be used for economic modelling rather than treatment-specific utilities.[16] The choice of treatment-specific utilities was not justified by the manufacturer. Given the approach to model treatment benefit, the model lacked flexibility as differences in treatment efficacy would not be explicitly linked to differences in QALYs. Treatment utility was calculated from those who remained in the study at week 24 post-transplant. Although completion rate of the EQ-5D questionnaire was similar in both arms (i.e., 64.2% and 58.3%, respectively, for letermovir and usual care at week 24), FDA requested reanalysis that included those who discontinued the trial. It was suggested that mortality would be higher when factoring in the patients who discontinued taking part in the trial and is indicative that they likely represent a population that is sicker.[17,18] Therefore, if treatment-specific utilities were calculated to account for those who discontinued being in the trial, the expected utility benefit associated with each treatment would be lower.
	Post-transplant (after first year): 0.76	The value in the model was 0.76 rather than the reported 0.82[26] in the PE report.[2] The manufacturer provided a source for this value during the review process. The value was considered old and came from a population different than the target population for letermovir (i.e., untreated multiple myeloma aged less than 65 years old undergoing autologous stem cell transplantation in years 1995 to 1999).[14] The utility weight post-transplant was not higher than the reported Canadian (Alberta) EQ-5D-3L norms for a 45- to 54-year-old individual (i.e., 0.798; SE = 0.008).[27]
Resource Use	Letermovir utilization based on the P001 trial.[3]	The average duration of treatment observed in Study P001 was 70 days.[3] Utilization was further based on [redacted]% receiving the oral regimen while the remaining [redacted]% received an IV for the first 9 days ([redacted]% on concomitant cyclosporine A and therefore, receiving the lower 240 mg dose of letermovir), followed by 240 mg oral letermovir for 61 days.[2] In the phase III RCT, treatment duration ranged from 1 to 113 days.[3] The PSA only tested a range of 63 to 77 days.[2] However, as the economic model was not sufficiently flexible, variation in treatment duration did not impact treatment efficacy. The clinical experts consulted as part of this review felt that there may be circumstances whereby letermovir may be used beyond

Data Input	Description of Data Source	Comment
		100 days. This could not be appropriately tested given the inflexibility in the manufacturer's model.
	PET regimen based on drug usage observed in the P001 trial.[2]	In the manufacturer's model, PET consisted of: 1) inpatient ganciclovir: 5 mg/kg daily (70 kg individual) for 29.2 inpatient days 2) outpatient valganciclovir: 900 mg daily for 30.1 outpatient days. Duration of treatment reflected the mean duration reported in Study P001. The PET regimen in model was not representative of Canadian setting. As per the medical literature and the feedback from the clinical experts, the regimen modelled was not representative of Canadian practice.[4] Rather, induction would consist of ganciclovir 5 mg/kg twice daily for 2 weeks (3 weeks if viremia remained present at week 2) and maintenance of ganciclovir 5 mg/kg daily for 4 weeks.[4] An alternative PET regimen was noted that would consist of valganciclovir 900 mg twice daily for six weeks.
Treatment-Related AEs	Incidence of PET-related AEs (i.e., neutropenia, thrombocytopenia, leukopenia) assumed to be 0	Incidence was assumed to be 0.[2] This assumption may not be appropriate given the lower proportion of patients requiring PET in the letermovir arm of the study. As such, it would be expected that the rates of AEs from PET would be lower in patients on letermovir.
	Letermovir-related AEs: Not considered in the economic model	Letermovir was not associated with significant additional toxicity in the phase III RCT.
Natural History (i.e., Mortality)	All-cause mortality at weeks 14 and 24 post-transplant: probabilities from P001 trial (full analysis set)[3]	All-cause mortality was an exploratory outcome in the clinical trial based on the full analysis set that included only patients who remained in the study and had not discontinued. The population in which this outcome was analyzed excluded 76 subjects who withdrew prematurely from the trial at week 24.[3] Although discontinuation was balanced between study arms, FDA requested reanalyses that included the vital statuses of 58 of the 76 patients who had discontinued taking part in the trial. This resulted in a higher mortality rate in both treatment arms (probability of death at 24 weeks: 12.1% for letermovir vs. 17.2% for usual care).[17,18] CDR conducted a scenario analysis with the FDA results on mortality outcomes.
	Mortality beyond first year post-transplant: Adjusting Canadian life tables[13] by an increased RR of death from a large multinational transplant patient registry[9]	According to the clinical experts consulted as part of this review, the selected transplant registry is generalizable to the Canadian transplant population. However, the manufacturer only selected a study that reported the relative risk of late mortality (i.e., 2 years to 15 years) for underlying disease in post-transplant patients compared with a general age-, gender-, and national-matched population. For the first year RR of death, it was assumed to be identical to the RR of death observed in the second year in the registry study.[2] This assumption

Data Input	Description of Data Source	Comment
		negates the fact that this international registry publication reported specifically on the long-term survival in patients who were alive and disease-free at year 2 (i.e., approximately 50% of the original cohort).[9] This assumption was inappropriate as it overestimated survival. Indeed, the model's predicted prevalence of death at year 2 (15% to 20%)[2] was lower than reported in the literature (~50% at year 3).[19] Furthermore, the RR of death were deterministic values that could not be varied in PSA. As the same approach to estimate life expectancy was applied to both strategies based on the proportion of patients still alive at week 24, this meant that the difference in mortality event rate between letermovir and usual care at week 24 was preserved when extrapolating the expected life expectancy of patients. Given the lack of long-term efficacy data on mortality between treatments (> 48 weeks), it is unclear whether this assumption would hold.
Drug Costs	Price of letermovir provided by the manufacturer and weighted daily drug costs were calculated based on the dosing regimen of P001 trial.[3] • Daily costs: $253.62	According to the clinical experts consulted as part of this review, the dosing regimen observed in the clinical trial is reflective of what would be expected in a Canadian setting. Although the manufacturer assumed treatment would be offered only during the first 100 days post-transplant, the treatment duration is uncertain. Clinical experts consulted as part of this CDR noted that it is expected that, in clinical practice, some patients may be treated for longer periods than is currently approved. Similarly, the published literature includes comments that letermovir prophylaxis may be offered for a duration of less than 100 days. CDR was unable to test the impact of alternative treatment durations due to restrictions in the model's structure. Furthermore, CDR was unable to replicate the manufacturer's daily drug cost calculation. In using information on study drug exposure at the 48-week period within the clinical study report (Table 14.3-1),[8] the average daily cost for letermovir was found to be $259.66.
	PET: Price of drugs from ODB[22] and overall treatment costs based on dosing regimen observed in P001 trial[3]	Unit cost for ganciclovir was incorrect. ODB cost is $43.9340 for a 500 mg vial. For a dose of 5 mg/kg in a 70 kg individual, CDR calculated that it would be $43.9340 (assuming the rest of the vial is discarded).[6] Note that in the phase III trial, average weight was 76.6 kg ± 17.4[3] whereas the manufacturer assumed a slightly lower average weight of 70 kg.
Administration Costs	IV, cost: Not included	Both letermovir and ganciclovir can be dosed by IV. Five per cent of patients in the P001 trial began with letermovir IV and the clinical experts consulted on this review felt the percentage of patients who would begin IV dosing would be low. Similarly, ganciclovir is a suitable PET regimen that would require IV administration.

Data Input	Description of Data Source	Comment
		Although not appropriate, the exclusion of IV costs would not likely impact the results.
	CMV disease monitoring costs: Assumed to be $0	As the CMV disease monitoring schedule was assumed identical in both arms, the manufacturer excluded these costs.
Event Costs	CMV disease: Assumed to be $0	Appropriate. The manufacturer stated that it was impossible to differentiate between CMV infection and CMV disease.[2] To prevent double-counting of costs, it was assumed the cases of CMV disease were likely included in the CMV-infection group.
	CMV-related hospitalization: CIHI's patient cost estimator and US claims study [2,7] • Costs: $29,164.75	Cost from CIHI's patient cost estimator for CMG 659 (chickenpox / herpes / CMV),[2] adjusted by a US claims study for length of study (i.e., 24.4 days).[7] Unit cost is appropriate. The clinical experts consulted as part of this review felt that the length of stay was reasonable. However, there is a concern that CMV-related hospitalizations were in fact GVHD-related hospitalizations. Several authors have highlighted the strong association ($P < 0.0001$) between CMV reactivation and GVHD.[28-32] In the absence of detailed breakdowns of the causes of hospitalizations within the phase III RCT, the costs of CMV-related hospitalizations, while kept in the CADTH base case, were removed in a scenario analysis.
	Opportunistic infections other than CMV-related (e.g., bacterial, fungal or other): CIHI's patient estimator[2] and analysis of P001 trial.[15] • Costs: $19,049.24	Costs of pneumonia and sepsis from CIHI, weighted from a post hoc analysis of types of infection that resulted in death in the P001 trial.[15] The post hoc analysis was specific to opportunistic infections resulting in death, which may not be a good representation of the types of manifestations for opportunistic infections (other than CMV-related) in the entire study population. Details on the weighting function were not provided to verify its appropriateness. CDR conducted a re-calculation using different data sources. Firstly, the clinical study report summarized the number of patients per type of infection and infectious agent at 48 weeks in Table 14.2-24.[8] According to this table, the most frequent opportunistic infections were: • bacteremia (42.3%) • urinary tract infection (mostly bacterial, (20.5%) • sepsis (mostly bacterial,19.6%) • pneumonia (17.2%). Using OCCI 2014-2015 for event costs, CDR calculated that the weighted average costs for opportunistic infections would be $9,290 ± $17,019, which was inflated to 2017 prices in the CADTH base-case reanalysis.[33]

Data Input	Description of Data Source	Comment
	GVHD: Ontario Drug Benefit [22] • Costs: $879.98	Drug costs to manage GVHD were calculated based on a regiment of methylprednisone 2 mg/kg daily for 40 days. This is consistent with usual practice in Canada as per the clinical experts consulted for this review.
	Annual costs after 1 year: Assumed to be $0	Inappropriate. As the model is driven by the long-term mortality benefit of letermovir, this assumption ignores the fact that post-transplant survivors will continue to incur medical costs beyond the first year. A Swedish study has shown that, although medical costs are highest in the first year of transplant, medical costs exist in subsequent years.[21] Costs were underestimated in both arms but, given the greater expected proportion of survivors on letermovir, this assumption favours letermovir.
Cost of Managing AEs	PET-related AEs: • neutropenia: $0 (as assumed to occur alongside leukopenia) • thrombocytopenia: $666.10 (Lagerquist et al. 2017, based on Cancer Care Ontario data) • leukopenia: $13,669.86 (Lagerquist et al. 2017, based on Cancer Care Ontario data)[2]	Appropriate. However, as incidence was assumed to be 0, these costs were not included in the manufacturer's base case.
	Letermovir-related AEs: not included	Letermovir has not been associated with significant toxicity in the P001 trial.
Health state	Decision-tree with 3 distinct post-transplant time periods: (i) 14 weeks: coincided with end of letermovir prophylaxis; the model evaluated mortality based on the P001 trial (ii) 24 weeks: coincided with a time point in which P001 trial evaluated CMV-related complications and change in patient management; the model evaluated these outcomes (iii) Lifetime: captured expected life expectancy (see *Mortality* for further details)	CMV-related complications and change in patient management were defined based on the clinical outcomes that were assessed in the trial. Based on the definitions for the clinical outcomes, there is uncertainty whether these outcomes in fact are mutually exclusive. Literature suggests some of the outcomes are not mutually exclusive and the clinical outcomes could be misclassified, given the high correlation between CMV-related hospitalization to GVHD and CMV infection.[28-32] There is a high risk of double-counting of event costs.

AE = adverse event; ALL = acute lymphocytic leukemia; AML = acute myelogenous leukemia; CDR = CADTH Common Drug Review; CIHI = Canadian Institute for Health Information; CMG = case mix group; CML = chronic myeloid leukemia, CMV = cytomegalovirus; EQ-5D = EuroQol 5-Dimensions; EQ-5D-3L = EuroQol 5-Dimensions 3-Level Questionnaire; GVHD = graft-versus-host disease; HSCT = hematopoietic stem cell transplant; IV = intravenous; MDS = myelodysplastic syndrome; NHL = non-Hodgkin lymphoma; OCCI = Ontario Case Costing Initiative; ODB = Ontario Drug Benefit; PCR = polymerase chain reaction; PE = pharmacoeconomic; PET = pre-emptive therapy; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; RCT = randomized controlled trial; RR = relative risk; SE = standard error.

Probabilistic sensitivity analysis was performed on the base case. Multiple one-way analyses were performed on the deterministic model. Although section 4.6 of the manufacturer's pharmacoeconomic report mentions that a sensitivity analysis with the 48-week study results was performed, the results of this scenario analysis was not presented in the results section. No other scenario analysis was performed.

Table 10: Manufacturer's Key Assumptions

Assumption	Comment
Death occurring during the trial period was assumed to occur at the mid-point of the time interval (i.e., between the 14-week to 24-week analyses, deaths occurred at 19 weeks, on average).	Reasonable in view of the type of model chosen
Patients who survived through the end of the trial period (i.e., 48 weeks) are assumed to survive to first year post-transplant.	Reasonable in view of the type of model chosen
The long-term mortality benefit from adding letermovir to usual care was assumed to remain constant over time (i.e., the difference in mortality event rate at week 24 of the study was preserved between treatment arms when extrapolating life expectancy).	Limited evidence was presented to support a difference in long-term mortality rates between treatments. The difference in mortality between the 2 treatment arms appears to diminish over the study period (estimated mortality difference of letermovir compared with usual care: −5.7% at week 24 and −4.6% at week 48).[3,8] Given the uncertainty with the potential long-term benefits of treatment, CDR conducted scenario analyses varying this assumption and it was found to be influential to the ICUR.
Mortality beyond the trial period (i.e., 1 year post-transplant) was assumed to be similar to the mortality reported from an international registry on late mortality in post-transplant survivors (i.e., 2 years to 15 years post-transplant). [9] First year post-transplant RR for death was assumed to be equal to the second year post-transplant RR for death. The RR of death after year 15 was assumed to be a constant value, based on the average RR from years 10 through 15.	The patient-transplant registry in which RR of long-term death was taken was deemed to be generalizable to the Canadian transplant population. Wingard et al. report that mortality following HSCT is high during the first 2 years as a result of relapse, GVHD, or infection, but long-term survival for year 2 survivors is excellent. In the cohort studied by Wingard et al., 15,543 of the 31,818 patients (49%) who had a HSCT had died or relapsed at 2 years. By applying the RR of death from year 2 to year 15, this greatly overestimated early survival (and underestimated mortality) and, therefore, overestimated the potential QALY gain for both letermovir with usual care and usual care alone. This assumption of the RR at year 1 approximating the RR at year 2 was deemed inappropriate and CDR reanalysis calibrated early mortality (< 3 years) to resemble the natural history of death reported in the same registry by another author.[19]
Patients on treatment had different first-year utility weights, based on their treatment assignment.	This contradicts modelling guidelines.[16] Although it may be partially justifiable given the differences in clinical efficacy in terms of the development of CMV-related complications, as utility weights were hard-coded to treatment, this did not allow the model to estimate QALYs if complication rates differed.
The duration of letermovir prophylaxis was 70 days.	This was based on the average duration of treatment observed in Study P001. This assumption could not be adequately tested by CDR as changes in treatment duration would impact only the estimated costs of treatment and would not consequently impact the incidence of CMV-related complications, which has both cost and clinical benefit impacts. According to the clinical experts, duration of treatment can extend beyond the 100 days recommended in the product monograph.[1]
Costs beyond 1 year were estimated to be 0.	This assumption was not considered reasonable by CDR as mortality was lower in the letermovir arm. Long-term costs were therefore underestimated with this assumption but, given the lack of Canadian published data, CDR could not conduct a reanalysis.

CDR = CADTH Common Drug Review; CMV = cytomegalovirus; GVHD = graft-versus-host disease; HSCT = hematopoietic stem cell transplant; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; RR = relative risk.

Additional CADTH Common Drug Review Reanalyses

The key limitations are presented in the main body of this report. In addition, several parameter values for the one-way and probabilistic analysis (i.e., distributions) were not appropriate. These included the following.

- **Probabilities of pre-emptive therapy (clinically significant cytomegalovirus infection in the model) and cytomegalovirus disease, at each time point and for each treatment arm:** The lower and upper limits of the 95% confidence interval (CI) reported in the P001 trial should have been used for the one-way sensitivity analysis values.[3,8] For the probabilistic analysis, the appropriate number of events should have been used to define the alpha and beta parameters in order to define the parameter distributions.
- **Letermovir treatment duration and daily costs:** The manufacturer's model assumed a standard deviation of 10% of the average value. However, within the clinical study report, tables 14.3-1 (24 weeks and 48 weeks), 12-2, and 12-23 report the range of treatment duration.[3,8] This would permit estimation of the potential variability in the duration of treatment which, when combined with the cost of letermovir, would allow estimation in the uncertainty with treatment costs.
- **Pre-emptive therapy costs:** The costs appear to be calculated based on a 70.0 kg individual while the study patients had an average weight of 76.6 kg.[3] This might have slightly underestimated costs and slightly favoured the usual care arm as pre-emptive therapy (PET) was more frequently prescribed in patients on usual care.
- **Pre-emptive therapy duration:** Similarly, the manufacturer's model assumed a standard deviation of 10% of the average value. However, within the clinical study report, Table 11-29 (24 weeks) reported that the PET duration was 59.3 ± 67.91 days (n = 120) for the entire cohort and, by treatment arms (60.4 ± 71.62 days [n = 52] in the letermovir with usual care arm and 58.5 ± 65.46 days [n = 68] in the usual care arm alone).[3] These values should have been used to define the parameter distribution as the assumptions taken would grossly underestimate variability.
- **Cost of opportunistic infection (other than cytomegalovirus-related):** The clinical study report summarized the number of patients per type of infection and infectious agent at 48 weeks in Table 14.2-24.[8] According to this table, the most frequent opportunistic infections were bacteremia (42.3%), urinary tract infection (mostly bacterial, 20.5%), sepsis (mostly bacterial, 19.6%), and pneumonia (17.2%). Using Ontario Case Costing Initiative values from 2014 to 2015 for event costs, CADTH Common Drug Review (CDR) recalculated that the weighted average costs for opportunistic infections would be $9,290 ± $17,019 (inflated to 2017 prices).[33]
- **Post-trial utility:** The utility value used by the manufacturer was felt to be inappropriate. We used the value of both treatment arms combined at week 48 from the phase III randomized controlled trial.[8]
- **Uncertainty in the long-term mortality estimates:** Variability in the RR of death associated with transplant survivors compared with a general population was not incorporated despite the fact that Wingard et al's publication reported a 95% CI in the relevant figures. [9] Given the inflexibility regarding how rates of RR were coded in the model, CDR could not introduce a probabilistic distribution for these parameters in the model.
- In response to these minor limitations and to the key limitations noted earlier in our report, Table 11 highlights the changes made to the model parameters between the manufacturer's submitted base case and CDR's base-case reanalysis while Table 12 details the one-way sensitivity analysis that was conducted regarding the key limitations as part of CDR's base case.

In addition, one of the clinical experts consulted in this review suggested that there may be a risk of misclassification of costs due to mutually non-exclusive health states**.** The manufacturer's submitted model was a decision-tree with the set of cytomegalovirus (CMV)-related complications and changes in patient management based on those reported in Study P001. The effects captured within decision-trees should be mutually exclusive, since the patient can only follow one pathway.[34] Given the definition of clinical outcomes within the trial, the selection of health outcomes captured in this model at 24 weeks could potentially not be mutually exclusive and could have resulted in double-counting of costs. As per the clinical experts consulted for this CDR, hospital admission is often due to graft-versus-host disease (GVHD). This is corroborated by a recent study that showed a strong association ($P < 0.0001$) between CMV reactivation and GVHD.[28] GVHD has been reported by several authors to be the main cost drivers in patients with CMV reactivation.[29-32] In the absence of detailed breakdowns of the causes of hospitalizations within the RCT, the extent to which costs may have been double-counted is unclear. In the case of GVHD, this limitation would introduce biases against the usual care arm, given it has higher probabilities of CMV-related hospitalization (mean difference at week 24 post-transplant: 4.8%) and GVHD (mean difference at week 24 post-transplant: 4.3%).

Table 11: Values Corrected as Part of CADTH Common Drug Review's Base Case

Parameter	Value	Lower Limit for One-Way Analysis	Upper Limit for One-Way Analysis	Alpha for PSA	Beta for PSA	Comment
Letermovir PET, 14 weeks	6.5%	3.7%	9.2%	21	304	Upper and lower bounds of 95% CI from the Kaplan–Meier analysis (Figure 11-3 from the P001 clinical study report at 24 weeks)[3]
Letermovir PET, 24 weeks	17.2%	12.8%	21.6%	56	269	Upper and lower bounds of 95% CI from the Kaplan–Meier analysis (Figure 11-3 from the P001 clinical study report at 24 weeks)[3]
Usual care PET, 14 weeks	40.2%	32.6%	47.9%	68	102	Upper and lower bounds of 95% CI from the Kaplan–Meier analysis (Figure 11-3 from the P001 clinical study report at 24 weeks)[3]
Usual care PET, 24 weeks	42.4%	34.7%	50.2%	72	98	Upper and lower bounds of 95% CI from the Kaplan–Meier analysis (Figure 11-3 from the P001 clinical study report at 24 weeks)[3]
Letermovir CMV disease, 14 weeks	0.3%	0.0%	1.0%	1	324	Upper and lower bounds of 95% CI from the Kaplan–Meier analysis (Figure 11-3 from the P001 clinical study report at 24 weeks)[3]
Letermovir CMV disease, 24 weeks	1.8%	0.2%	3.4%	6	319	Upper and lower bounds of 95% CI from the Kaplan–Meier analysis (Figure 11-3 from the P001 clinical study report at 24 weeks)[3]
Usual care CMV disease, 14 weeks	1.3%	0.0%	3.0%	2	168	Upper and lower bounds of 95% CI from the Kaplan–Meier analysis (Figure 11-3 from the P001 clinical study report at 24 weeks)[3]
Usual care CMV disease, 24 weeks	2.1%	0.0%	4.4%	4	166	Upper and lower bounds of 95% CI from the Kaplan–Meier analysis (Figure 11-3 from the P001 clinical study report at 24 weeks)[3]
Daily letermovir costs	$259.66	$251	$503			Calculated based on Table 14.3-1 (48 weeks) from the P001 clinical study report[8] and the costs of letermovir provided by the manufacturer.[2]

Parameter	Value	Lower Limit for One-Way Analysis	Upper Limit for One-Way Analysis	Alpha for PSA	Beta for PSA	Comment
						Dose range: 240 mg IV/oral to 960 mg oral. This parameter could not be tested in the PSA, given the manner in which it is coded in the model.
Letermovir treatment duration	70 days	33.4	106.6			In phase III RCT (i.e., Study P001), treatment duration with letermovir ranged between 1 and 113.[3] Assuming this represents 99.7% of the CI, the SE can be estimated at 18.7 days. Note: Changes in the treatment duration for letermovir only impacted the cost of treatment and had no impact on efficacy.
PET induction costs	$87.86/day					This was based on dosage of 5 mg/kg for a 70 kg individual (i.e., 350 mg) twice daily, using $43.93 per 500 mg vial and assuming leftover is discarded. This value is not varied in the PSA (official tariff).[6]
PET induction duration	14 days	11.7	16.2			As per clinical practice in Canada, i.e., 14 days (21 days if positive viremia at day 14) and assuming range of 14 days to 21 days, this represents 99.7% CI; SE = 1.2.
PET maintenance costs	$43.93/day					This value is not varied in the PSA (official tariff).[6]
PET maintenance duration	28 days					This value is not varied in the PSA.
Cost of opportunistic infection	$10,058					Based on weighted average of 2014-2015 OCCI values for bacteremia, pneumonia, sepsis, and UTIs and inflated to 2017 prices; SE = $868.[33]
Post-trial utility	0.768	0.703	0.834			As per week-48 value from phase III RCT (i.e., Study P001).[8]
Usual care all-cause mortality at 1 year	20.5%					As per week-48 value from phase III RCT (i.e., Study P001).[8]
Usual care survival at 3 years	51.25%					Weighted average of 3-year values reported in Teira et al. in R+ patients, assuming myelofibrosis and plasma cell myeloma have similar survival to that of MDS and severe aplastic anemia, CLL, and lymphoma have similar survival to that of CML.[19]
Usual care survival rate at 2 years	61.79%					Interpolated from year 1 and year 3 values by log transformation.

CI = confidence interval; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; CMV = cytomegalovirus; IV = intravenous; MDS = myelodysplastic syndrome; OCCI = Ontario Case Costing Initiative; PET = pre-emptive therapy; PSA = probabilistic sensitivity analysis; R+ = cytomegalovirus-seropositive recipients; RCT = randomized controlled trial; SE = standard error; UTI = urinary tract infection.

Table 12: CADTH Common Drug Review One-Way Sensitivity Analysis to Evaluate the Limitations Identified to the Manufacturer's Model

Scenario	Element	Treatments (Difference)	Total Costs	Total QALY	ICUR
	Manufacturer's base case	Letermovir, taken with usual care	$28,535	7.88	
		Usual care	$14,062	7.36	
		Incremental	$14,473	0.52	$27,990/QALY
A	Letermovir, 14-week PET usage	Letermovir, taken with usual care	$28,555	7.88	
		Usual care	$14,081	7.37	
		Incremental	$14,474	0.51	$28,200/QALY
B	Letermovir, 24-week PET usage	Letermovir, taken with usual care	$26,640	7.88	
		Usual care	$14,105	7.36	
		Incremental	$12,535	0.53	$23,764/QALY
C	Usual care, 14-week PET usage	Letermovir, taken with usual care	$26,658	7.88	
		Usual care	$14,081	7.37	
		Incremental	$12,577	0.51	$24,507/QALY
D	Usual care, 24-week PET usage	Letermovir, taken with usual care	$26,694	7.88	
		Usual care	$12,381	7.37	
		Incremental	$14,313	0.51	$27,820/QALY
E	Letermovir, 14-week CMV disease	Letermovir, taken with usual care	$26,631	7.88	
		Usual care	$12,389	7.37	
		Incremental	$14,242	0.51	$27,869/QALY
F	Letermovir, 24-week CMV disease	Letermovir, taken with usual care	$26,606	7.89	
		Usual care	$12,379	7.37	
		Incremental	$14,227	0.51	$27,657/QALY
G	Usual care, 14-week CMV disease	Letermovir, taken with usual care	$26,610	7.89	
		Usual care	$12,376	7.36	
		Incremental	$14,234	0.52	$27,246/QALY
H	Usual care, 24-week CMV disease	Letermovir, taken with usual care	$26,627	7.88	
		Usual care	$12,391	7.37	
		Incremental	$14,236	0.51	$27,680/QALY
I	Daily letermovir costs	Letermovir, taken with usual care	$27,020	7.88	
		Usual care	$12,369	7.37	
		Incremental	$14,651	0.51	$28,469/QALY
J	Letermovir treatment duration	Letermovir, taken with usual care	$27,146	7.89	

Scenario	Element	Treatments (Difference)	Total Costs	Total QALY	ICUR
		Usual care	$12,387	7.37	
		Incremental	$14,759	0.52	$28,657/QALY
K	PET induction costs	Letermovir, taken with usual care	$25,874	7.88	
		Usual care	$9,640	7.37	
		Incremental	$16,234	0.52	$31,517/QALY
L	PET induction duration	Letermovir, taken with usual care	$25,581	7.88	
		Usual care	$8,108	7.37	
		Incremental	$16,473	0.51	$32,336/QALY
M	PET maintenance costs	Letermovir, taken with usual care	$25,946	7.88	
		Usual care	$9,507	7.37	
		Incremental	$16,439	0.51	$32,133/QALY
N	PET maintenance duration	Letermovir, taken with usual care	$25,830	7.88	
		Usual care	$9,489	7.36	
		Incremental	$16,341	0.52	$31,267/QALY
O	Opportunistic infection costs	Letermovir, taken with usual care	$23,065	7.88	
		Usual care	$6,779	7.37	
		Incremental	$16,285	0.51	$31,793/QALY
P	Post-trial utility	Letermovir, taken with usual care	$23,055	7.96	
		Usual care	$6,762	7.44	
		Incremental	$16,293	0.52	$31,298/QALY
Q	Usual care, year 1 and year 2 survival (**CADTH base-case reanalysis**)	Letermovir, taken with usual care	$23,088	5.10	
		Usual care	$6,757	4.78	
		Incremental	$16,331	0.32	$51,052/QALY

CMV = cytomegalovirus; ICUR = incremental cost-utility ratio; PET = pre-emptive therapy; QALY = quality-adjusted life-year.

The CDR base-case reanalysis and select scenario analyses that explored alternative long-term mortality benefits associated with letermovir and alternative PET regimens are presented in the main body of our report. In addition, CDR tested additional scenario analyses that explored alternative time horizons, mortality differences between letermovir with usual care compared with usual care alone, patient age, PET regimens (i.e., different drugs, dosage, and duration of induction treatment) and costs of letermovir.

Varying time horizons:

- Scenario 4: Modelled time horizon of 14 weeks
- Scenario 5: Modelled time horizon of 24 weeks
- Scenario 6: Modelled time horizon of 48 weeks

Different parameters that impact the relative mortality differences between treatments:

- Scenario 7: Lifetime analysis based on 48-week values reported in the P001 trial (i.e., RR of death for letermovir with usual care compared with usual care alone = 0.94)
- Scenario 8: Year 1 and year 2 survival data (52.05% and 41.82%, respectively), based on a publication by Majhail et al.[20]
- Scenario 9: Week 24 death rates as per FDA reanalyses (letermovir with usual care: 12.1% [95% CI: 8.6 to 15.7]; usual care alone: 17.2% [95% CI: 11.5 to 22.9][17,18])

Age of patient cohort:

- Scenario 10: Upper limit of 95% CI for age reported in P001 trial (78 years old)
- Scenario 11: Lower limit of 95% CI for age (18 years old)

PET regimens:

- Scenario 12: PET regimen defined as valganciclovir, 900 mg once daily for six weeks
- Scenario 13: PET regimen defined as valganciclovir, 900 mg once daily for 100 days
- Scenario 14: PET regimen defined as valganciclovir, 900 mg twice daily for 100 days
- Scenario 15: Duration of PET induction phase defined as three weeks

Treatment costs for letermovir:

- Scenario 16: Letermovir treatment duration of 100 days (includes only impact costs of treatment, not parameters relating to treatment efficacy)
- Scenario 17: Upper limit of daily letermovir costs ($503), if assuming the patient received 960 mg, the maximum dosing reported in the clinical study report[3,8]
- Scenario 18: Lower limit of daily letermovir costs ($251)

Adjusting for non-mutually exclusive health states:

- Scenario 19: CMV-related hospitalization costs removed

Table 13: Additional Scenario Analyses

Scenario	Element	Treatments (Difference)	Total Costs	Total QALY	ICUR
Manufacturer's base case		Usual care	$14,062	7.36	
		Letermovir, taken with usual care	$28,535	7.88	
		Incremental	$14,473	0.52	$27,990/QALY
Full CADTH base case		Usual care	$6,757	4.78	
		Letermovir, taken with usual care	$23,088	5.10	
		Incremental	$16,331	0.32	$51,052/QALY
Scenarios that varied time horizon					
4	Modelled time horizon of 14 weeks	Usual care	$5,685	0.17	
		Letermovir, taken with usual care	$21,121	0.20	
		Incremental	$15,436	0.02	$667,174/QALY
5	Modelled time horizon of 24 weeks	Usual care	$6,755	0.30	
		Letermovir, taken with usual care	$22,979	0.33	
		Incremental	$16,224	0.04	$453,248/QALY
6	Modelled time horizon of 48 weeks	Usual care	$7,852	0.58	
		Letermovir, taken with usual care	$23,936	0.67	
		Incremental	$16,084	0.09	$176,982/QALY
Scenarios that varied parameters impacting relative mortality difference between treatment					
7	Lifetime analysis using 48-week clinical results from P001 trial	Usual care	$7,860	4.33	
		Letermovir, taken with usual care	$23,929	4.60	
		Incremental	$16,069	0.27	$59,359/QALY
8	Year 1 and year 2 survival from a US study[20]	Usual care	$6,727	3.75	
		Letermovir, taken with usual care	$23,133	4.01	
		Incremental	$16,406	0.26	$64,044/QALY
9	24-week death rates as per FDA reanalysis[17,18]	Usual care	$23,128	4.70	
		Letermovir, taken with usual care	$6,744	4.99	
		Incremental	$16,384	0.29	$56,238/QALY
Scenario that varied cohort's age					
10	Age of cohort: 78 years old	Usual care	$6,759	1.86	
		Letermovir, taken with usual care	$23,085	1.99	
		Incremental	$16,326	0.13	$129,576/QALY
11	Age of cohort: 18 years old	Usual care	$6,756	10.00	
		Letermovir, taken with usual care	$23,102	10.68	
		Incremental	$16,346	0.68	$24,172/QALY
Scenarios that varied PET regimen					

Scenario	Element	Treatments (Difference)	Total Costs	Total QALY	ICUR
12	Valganciclover, 900 mg daily for 6 weeks	Usual care	$5,931	4.78	
		Letermovir, taken with usual care	$22,839	5.10	
		Incremental	$16,908	0.32	$52,918/QALY
13	Valganciclover, 900 mg daily for PET maintenance	Usual care	$6,398	4.78	
		Letermovir, taken with usual care	$22,953	5.10	
		Incremental	$16,555	0.33	$50,904/QALY
14	Valganciclover, 900 mg twice daily for PET maintenance	Usual care	$6,500	4.78	
		Letermovir, taken with usual care	$22,853	5.10	
		Incremental	$16,353	0.32	$50,941/QALY
15	Duration of induction: 3 weeks	Usual care	$7,025	4.78	
		Letermovir, taken with usual care	$23,014	5.10	
		Incremental	$15,988	0.32	$49,348/QALY
Scenarios that varied cost of letermovir					
16	Letermovir treatment, duration at 100 days	Usual care	$6,762	4.78	
		Letermovir, taken with usual care	$30,724	5.10	
		Incremental	$23,962	0.32	$73,940/QALY
17	Daily cost of letermovir: $503	Usual care	$6,746	4.78	
		Letermovir, taken with usual care	$40,123	5.10	
		Incremental	$33,377	0.32	$103,436/QALY
18	Daily cost of letermovir: $251	Usual care	$6,754	4.78	
		Letermovir, taken with usual care	$22,474	5.10	
		Incremental	$15,720	0.32	$40,603/QALY
Scenario that adjusted for non-mutually exclusive health states					
19	No CMV-related hospitalizations	Usual care	$4,526	4.78	
		Letermovir, taken with usual care	$22,354	5.10	
		Incremental	$17,828	0.32	$54,940/QALY

CMV = cytomegalovirus; ICUR = incremental cost-utility ratio; PET = pre-emptive therapy; QALY = quality-adjusted life-year.

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