5.07 LETERMOVIR, Tablet 240mg, Prevymis™ Merck Sharpe & Dohme Australia

1 Purpose of Application

1.1 The submission requested a Section 100 Authority Required listing for letermovir for prophylaxis of cytomegalovirus (CMV) infection or disease in CMV sero-positive patients who have received an allogeneic haematopoietic stem cell transplant (HSCT).

1.2 The draft PI indicates that letermovir is available in two formulations, film-coated tablets containing 240 mg or 480 mg of letermovir and concentrate for solution for infusion containing 240 mg or 480 mg of letermovir. The oral and intravenous (IV) formulations of letermovir may be used interchangeably with no dose adjustment required when switching between the formulations. Only the tablets containing 240 mg of letermovir have been requested for listing in this submission.

1.3 Listing was requested on the basis of a cost utility analysis versus placebo. The key components of the clinical issue addressed by the submission are presented in Table 1.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT).
Intervention	Letermovir 240mg/day is used concomitantly with cyclosporin (480mg/day if used alone) through 100 days post-transplant. The submission also stated (Table 1-1, p8) that letermovir would be added to standard of care pre-emptive treatment for active CMV infection as required.
Comparator	Placebo.
Outcomes	Prevention of clinically significant CMV infection and improved survival.
Clinical claim	Letermovir is superior in terms of efficacy and has non-inferior safety in the prophylaxis of CMV infection or disease in adult CMV-seropositive recipients of an allogeneic HSCT compared to placebo.

Source: Table 1-1, p8 of the submission.

2 Requested listing

The Secretariat's suggested additions are *in italics* and deletions are ~~in strikethrough~~.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
Letermovir 240mg tablet, 28 tablets	1	3	$[redacted]	PREVYMIS	MSD AUSTRALIA

Category / Program	Section 100 – Highly Specialised Drugs Program *(Private and Public Hospitals)*
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives

Condition:	~~Allogeneic haematopoietic stem cell transplant~~ *Cytomegalovirus infection and disease*
PBS Indication:	~~Prophylaxis of CMV~~ *Cytomegalovirus* infection ~~or~~ *and* disease
Treatment phase:	~~Initial~~ *Prophylaxis*
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing (Public/Private) ☒ Authority Required – Telephone (Public/Private) ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☒ *Streamlined* (Public only)
Clinical criteria:	Patient must have ~~received~~ *undergone, ~~be undergoing~~ or be scheduled to receive ~~for~~* an allogeneic haematopoietic stem cell transplant~~;~~ AND The patient must have confirmed presence of ~~CMV~~ *cytomegalovirus* -specific antibodies ~~(confirmed seropositivity)~~.
Prescriber Instructions	*For patients who are not concurrently taking cyclosporin and letermovir, two packs of 28 tablets will need to be requested and authorised for dispensing.*
Administrative Advice	No increase in the maximum number of repeats will be authorised ~~For patients who are not concurrently taking cyclosporin and letermovir, two packs of 28 tablets will need to be requested and authorised for dispensing.~~ ~~Note: As an Authority Required medication, physicians will be required to provide whether the patient is concurrently taking cyclosporin. For patients who are not concurrently taking cyclosporin and letermovir, two packs of 28 tablets will need to be requested and authorised for dispensing. This is estimated to impact ~7% of patients treated with letermovir.~~

2.1 The submission stated that PBS listing is sought under the Highly Specialised Drugs (HSD) program, as 'Public Hospital Authority Required' and 'Private Hospital Authority Required'. The submission indicated that while letermovir is not for chronic treatment, having letermovir as a HSD would be appropriate as this therapy is likely to be dispensed in a hospital outpatient setting on the advice of specialists. The proposed restriction is like to be considered a non-Complex Authority Required (CAR) listing. A STREAMLINED Authority is appropriate for non-CAR HSD listings in the public hospital setting. The Pre-Sub-Committee Response (PSCR) accepted the commentary feedback and is agreeable to aligning the requested restriction according to the changes proposed by the Secretariat.

2.2 The submission added that clinician feedback has indicated that some HSCT recipients are treated solely in an outpatient setting and are not admitted for a transplant procedure. On this basis, the submission requested that the number of repeats be sufficient to allow for at least 100 days of treatment. The requested restriction will allow for 112 days of treatment, which is greater than the recommended 100 days of treatment, although with a pack size of 28 tablets it would not be possible to obtain concurrence with the recommended 100 days of treatment. The submission provided no indication of the likely proportion of patients who would be treated solely in an outpatient setting.

2.3 The submission stated that a similar example of such dispensing behaviour is seen with eculizumab (Soliris) for the treatment of patients with atypical haemolytic uraemic syndrome (aHUS) in end stage renal disease who are eligible for a renal

transplant. In this situation, the PBAC indicated that in-patient treatment should not be subsidised by the PBS (paragraph 7.2, July 2017 eculizumab Public Summary Document). The submission has requested to follow the precedence of eculizumab use in-hospital, and maintained that pre-approval and drug delivery in advance of transplant is possible and is likely to occur as the high cost of allogeneic HSCT incurred by the hospital is expected to prohibit further spending in this patient population. The July 2017 recommendation for the treatment of patients with aHUS in end stage renal disease who are eligible for a renal transplant has not yet been listed on the PBS, so the final circumstance of the eculizumab restriction is not known. The Secretariat noted in the Commentary that is was not clear what this submission is requesting in regards to how letermovir is made available to a patient. This issue was not addressed in the PSCR.

2.4 DUSC discussed several issues where the proposed restriction did not align with the clinical criteria in the P001 trial and the draft Product Information (PI):

- DUSC noted that although the draft PI stated that letermovir should be continued through 100 days post-transplant, the maximum duration of therapy of letermovir was not specified in the restriction. The sponsor highlighted that it would be unlikely for patients to continue treatment beyond 100 days. However, DUSC noted that there is potential that the duration of treatment for letermovir may be longer in some patients due to the potential for rebound viraemia.
- In the P001 trial, letermovir was ceased if CMV infection developed. However, this was not specified in the draft PI or in the proposed restriction.
- The draft PI (concurrent with the P001 key inclusion criteria) stated that letermovir may be started on the day of transplant and no later than 28 days post-transplant. DUSC pointed out that this was not specified in the proposed restriction.
- DUSC considered that patients who are CMV-seronegative may have a donor who is CMV-seropositive and noted that the restriction did not specify when testing for CMV-specific antibodies is to be undertaken.
- Patients who had detectable CMV infection were excluded from the P001 trial. This was not mentioned in the proposed restriction or in the draft PI. This allows for use in patients with CMV infection where safety and effectiveness have not been established.
- DUSC expressed concern that while the safety and efficacy of letermovir has not been established in paediatric patients under the age of 18 years, the proposed restriction did not impose age restrictions.

2.5 The ESC and DUSC noted that the TGA Delegate Overview includes the proposed registration of 'concentrated injection for infusion vial'. The ESC requested that the sponsor includes in the pre-PBAC response an indication of whether the intravenous (IV) form of letermovir will be made available in Australia for use in a hospital setting. The ESC noted that severe mucositis and / or diarrhoea can occur in patients

following allogeneic haematopoietic stem cell transplant (HSCT), where oral letermovir for 1-2 weeks may not be appropriate. If a patient was to receive intravenous letermovir for a period of time, the dispensing of 112 tablets as per the proposed listing would likely result in wastage.

2.6 The Pre-PBAC response accepted the DUSC feedback and was agreeable to aligning the requested restriction according to the issues raised by DUSC. In addition, the Pre-PBAC response advised that the IV formulation of letermovir will be made available for use in a hospital setting. It is not expected that the use of the IV formulation will increase the likelihood of wastage, as patients will receive IV letermovir as an inpatient following the transplant procedure and are then expected to be discharged with letermovir tablets when they are able to tolerate oral formulations. The appropriate quantity of repeats to ensure therapy up to 100 days post-transplant is expected to be requested upon prescribing letermovir on discharge in these patients.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Background

Registration status

3.1 The submission was made under the TGA/PBAC parallel process. At the time of the PBAC consideration, letermovir was registered on the ARTG (22 June 2018). At the time of ESC Advice, an extract of the round 2 Clinical Evaluation Report (CER) and the TGA Delegate's Overview were available. At the time of the evaluation, the round 1 CER was available.

3.2 The submission stated that letermovir has been granted regulatory approval in the USA (November 2017), Canada (November 2017) and the European Union (January 2018). The TGA Delegate's Overview stated the advice of the Advisory Committee on Medicines was not sought for this TGA submission, as the evaluations by the TGA and overseas assessment reports were deemed to be sufficient.

3.3 The final Product Information states:

- Indication is for the prophylaxis of cytomegalovirus (CMV) infection or disease in adult CMV seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT).'
- The recommended dosage of PREVYMIS is 480 mg administered once daily.
- PREVYMIS should be started after HSCT. PREVYMIS may be started on the day of transplant and no later than 28 days post-transplant. PREVYMIS may be started before or after engraftment. Continue PREVYMIS through 100 days post-transplant

- PREVYMIS tablet and concentrated injection for infusion may be used interchangeably at the discretion of the physician, and no dose adjustment is necessary.
- If PREVYMIS is co-administered with cyclosporin, the dosage of PREVYMIS should be decreased to 240 mg once daily

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 CMV infection or CMV viraemia refers to the presence of viral proteins or nucleic acid in body fluids or tissue. It has been estimated that CMV infects between 40% to 90% of all individuals worldwide. Following initial infection, CMV establishes a life-long latent infection in the host. Individuals who carry latent CMV are sero-positive. A sero-survey of CMV in Australia demonstrated that the population-weighted rate of CMV sero-positivity in individuals aged between 1 to 59 years was 57%.

4.2 Following haematopoietic stem cell transplant (HSCT) patients are at risk of developing opportunistic infections such as CMV due to the immunosuppressive regimens used as part of the transplant process. CMV infection has been associated with an increased risk of bacterial and fungal infections, graft rejection, increased health care costs and decreased survival.

4.3 CMV infection is currently managed with prophylactic treatment with antiviral medications, which the submission stated was limited by toxicities with the use of these agents such as ganciclovir. CMV infection has also been managed with the use of pre-emptive therapy (PET) which consists of the use of antivirals following detection of CMV and aims to treat the detected CMV infection and prevent development of symptoms and CMV disease.

4.4 Letermovir is proposed for use as prophylactic therapy for CMV infection, with treatment commencing within 28 days of HSCT.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated placebo as the main comparator as the majority of patients in Australia do not receive prophylaxis for CMV infection following HSCT. To support this claim the submission cited data from the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR[1]) which indicated that [redacted]% of Australian patients receive a prophylaxis strategy using ganciclovir following HSCT. The

[1] The ABMTRR records details of bone marrow, peripheral blood and cord blood stem cell transplants throughout Australia and New Zealand. The data in Attachment 1 of the submission was based on adult allogeneic hematopoietic cell transplants performed in Australia in 2014 to 2016.

ABMTRR data provided with the submission indicated that approximately [redacted]% of CMV sero-positive patients had used ganciclovir for CMV prophylaxis (Table 9, Attachment 1 of the submission). The submission also stated that clinician feedback was sought and this feedback universally indicated a lack of routine prophylaxis in Australian transplant centres, and that clinicians report that the toxicities experienced with current anti-CMV agents prohibit prophylaxis in this patient group. The submission did not provide any information on the how this clinician feedback was sourced, or how many clinicians provided feedback. The PBAC noted that PET became possible since the development of quantitative PCR assays.

5.2 PBS statistics for use of ganciclovir for CMV prophylaxis (PBS items 5749N and 6136Y) indicated that there were 259 services in 2016 and 300 in 2017. The submission estimated a patient population of 375 patients in Year 1 for letermovir with each patient using 3.21 packs per year (1 pack per script). Since the ganciclovir PI indicates dosing is on an individual case-by-case basis (i.e. 10 mg/kg for 14 to 21 days for induction and 5mg/kg once daily 7 days per week or 6mg/kg once daily for 5 days per week for maintenance) and the drug is supplied as 5 vials of a 500mg injection, the current PBS statistics for ganciclovir as prophylaxis (e.g. 300 scripts in 2017) would match usage for 60 patients assuming PI dosing is used and an average weight of 80kg per patient which, was 16% of the 375 patients estimated by the submission to be treated with letermovir in Year 1 of PBS listing.

5.3 Other agencies (e.g. NICE[2]) are including antivirals (aciclovir and valaciclovir) as comparators for letermovir. The ABMTRR data provided with the submission indicated that approximately [redacted]% of CMV sero-positive patients and approximately [redacted]% of CMV sero-negative patients had used aciclovir, valaciclovir or valganciclovir for CMV prophylaxis (Table 9, Attachment 1 of the submission). In this Table 9, 'Recipient CMV status' nor 'CMV prophylaxis' was not reported for [redacted] patients of the total [redacted] patients ([redacted]%).

5.4 The evaluation considered it was reasonable to use placebo as the comparator, as there is limited use of ganciclovir as prophylaxis for CMV infection following HSCT.

5.5 The ESC noted that currently only high risk patients receive prophylaxis for CMV post -allograft and use is this population is variable. For this small patient population, comparators could include acyclovir, valaciclovir and ganciclovir. However, the ESC agreed with the submission and the evaluation that in the overall proposed patient population, it was reasonable to use placebo as the comparator.

5.6 The PBAC noted the evidence, such as the ABMTRR report, showed that antiviral treatments are used in Australian practice, either prophylactically or as PET, and their use would likely reduced with the availability of letermovir. The PBAC

[2] Final scope available at: https://www.nice.org.uk/guidance/gid-ta10195/documents/final-scope

considered that both placebo and antiviral treatments would be informative comparators.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed the risk factors for CMV Infection or CMV reactivation and resulting CMV-associated clinical complications for patients after a transplant. The clinician summarised recent clinical experience in their institution and presented a clinical case study of the impact of CMV on a patient following an allogeneic HSCT. In response to the Committee's questions, the clinician addressed other matters about the current antiviral treatments and noted that the clinical evidence supported a reduction in the use of pre-emptive therapy (PET) but no difference in the incidence of graft versus host disease (GVHD) with letermovir treatment.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (3) via the Consumer Comments facility on the PBS website. The comments described their experiences with the issues that arise with the current treatment options and their views on the advantages of having an effective prophylactic therapy.

Clinical trials

6.3 The submission was based on Trial P001, a randomised, double-blind Phase III trial comparing letermovir and placebo in CMV sero-positive patients who had received an allogeneic HSCT. There appeared to be a limited number of letermovir trials available, with only three trials listed on clinicaltrials.gov, and one of those trials in kidney transplant patients, which was not relevant to the requested restriction. The other available trial was a Phase II letermovir trial which assessed letermovir dosing in sero-positive allogeneic HSCT recipients. The submission indicated that this Phase II trial was excluded from consideration because of the availability of Phase III data from Trial P001.

6.4 While it may be reasonable to focus on the available Phase III data, given the limited available data for letermovir it would have been informative for the submission to provide a summary of information from the Phase II trial. A brief summary of results from the Phase II trial is presented below under 'Comparative effectiveness'.

6.5 Clinical study report and publication details of Trial P001 are provided in the table below.

Table 2: Trial and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
P001	A Phase III Randomized, Placebo-controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-8228 (Letermovir) for the Prevention of Clinically Significant Human Cytomegalovirus (CMV) Infection in Adult, CMV-Seropositive Allogeneic Hematopoietic Stem Cell Transplant Recipients	May 2017
	Marty FM, Ljungman P, Chemaly RF, Maertens J, et al. Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation.	NEJM 2017; 377(25):2433-2444

Source: Table 2-2, p33-34 of the submission.

6.6 The key features of Trial P001 are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Trial P001	565[a]	R, DB, MC 14 weeks treatment and follow-up through 48 weeks	Low	CMV sero-positive patients who were recipients of an allogeneic HSCT	CMV infection, CMV disease, mortality, GVHD, QoL	CMV infection, CMV disease, mortality, GVHD

[a] While there were 565 patients randomised, the analysis population consisted of only 495 patients as 70 patients with detectable CMV DNA on Day 1 were excluded.

CMV=cytomegalovirus; DB=double blind; GVHD=graft versus host disease; HSCT=haematopoietic stem cell transplant; MC=multi-centre; QoL=quality of life; R=randomised

Source: Sections 2.2.3 to 2.4, p32-46 of the submission.

6.7 While there were 565 patients randomised to treatment in Trial P001, the analysis population consisted of only 495 patients as 70 patients with detectable CMV DNA on Day 1 were excluded. This patient group is consistent with population defined by the proposed listing.

6.8 In Trial P001 51.9% of patients received concomitant treatment with cyclosporin. In the economic model and financial impact estimates, the submission applied data from the ABMTRR which indicated that [redacted]% of Australian patients used cyclosporin. When used with cyclosporin, letermovir is dosed at 240mg/day while when used alone, it is dosed at 480mg/day.

6.9 The primary outcome in Trial P001 was the proportion of patients with clinically significant CMV infection at Week 24, comprised of onset of CMV end-organ disease or initiation of pre-emptive therapy (PET) based on documented CMV viraemia and the clinical condition of the patient. The primary outcome was assessed on a non-completer equals failure basis, where any patient who discontinued or had missing data was considered a failure. The submission also provided results for the exploratory outcomes of all-cause mortality, GVHD and quality of life outcomes (EQ-5D and FACT-BMT). The ESC considered these were appropriate outcome measures for assessing the comparative effectiveness of letermovir.

Comparative effectiveness

6.10 The table below provides results for the primary outcome in Trial P001, the proportion of patients with clinically significant CMV infection.

Table 4: Results for the primary outcome in Trial P001 – proportion of patients with clinically significant CMV infection at Week 24

	Letermovir (N=325) n %	Placebo (N=170) n %
Clinically significant CMV infection by Week 24	57 (17.5%)	71 (41.8%)
Initiation of PET	52 (16.0%)	68 (40.0%)
CMV end-organ disease	5 (1.5%)	3 (1.8%)
Discontinued before Week 24	56 (17.2%)	27 (15.9%)
Missing outcome in Week 24 visit window	9 (2.8%)	5 (2.9%)
Total failures[a]	122 (37.5%)	103 (60.6%)
Stratum-adjusted treatment difference (95% CI)	**-23.5% (-32.5, -14.6)**	

[a] As the analysis assumed non-completers equals failure, this total includes patients with CMV infection as well as those who discontinued or were missing outcome data at Week 24.

CI=confidence interval; CMV=cytomegalovirus; PET=pre-emptive therapy; **bold**=statistically significant

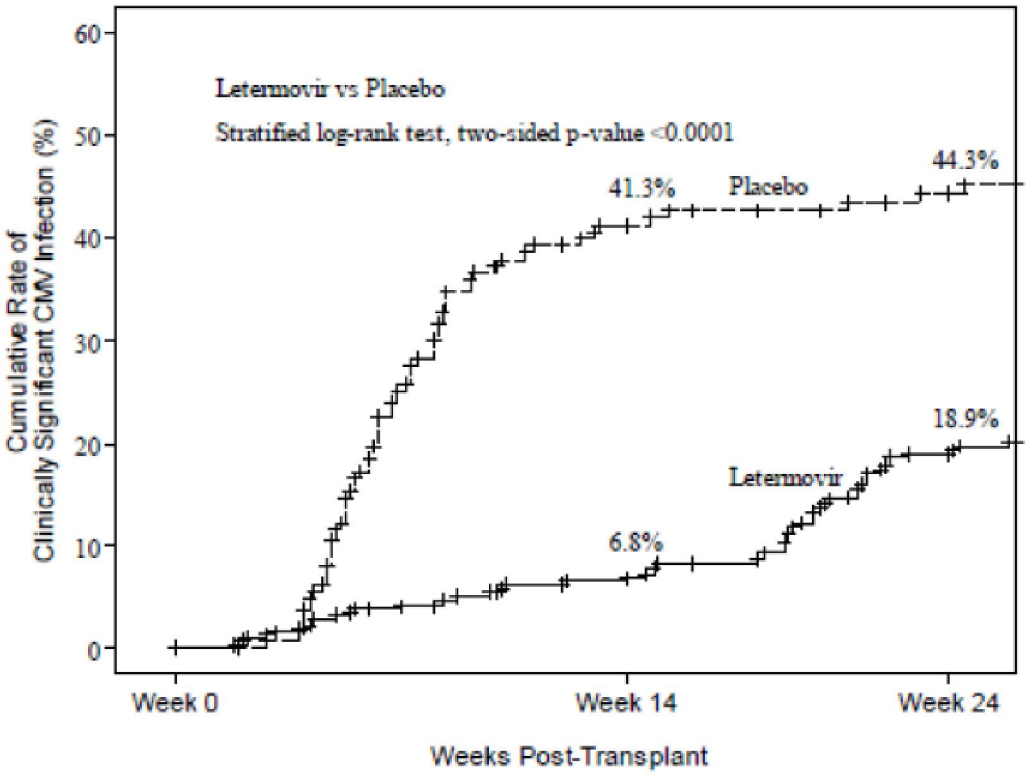
Source: Table 2-9, p49 of the submission.

6.11 With the analysis adjusted for low- and high-risk patients (risk of CMV reactivation), the analysis demonstrated a statistically significantly lower risk of CMV infection for patients treated with letermovir. With those who discontinued considered failures in the analysis, the proportion with documented CMV infection was 17.5% in the letermovir group and 41.8% in the placebo group.

6.12 The submission also presented results for the proportion of patients with clinically significant CMV infection for the subgroup of patients using cyclosporin. These results also demonstrated a statistically significant advantage for letermovir, with a stratum-adjusted treatment difference of [redacted]% (95% CI: [redacted], [redacted]). While these results demonstrated significantly less CMV infection in letermovir-treated patients also taking cyclosporin compared to placebo-treated patients, the analysis presented by the submission was based on the 'data as observed' population, where patients with missing data were excluded from the analysis. This differed from the non-completer=failure approach used for the primary outcome measure.

6.13 Not discussed in the main body of the submission, but raised in the first round CER from the TGA, was that when treatment was stopped at Week 14 (day 98) post-transplant there were few further cases of CMV infection in the placebo group while there was a significant increase in the letermovir group. The CER requested that the sponsor comment on the disparity and the potential for rebound viraemia. The Kaplan-Meier plot from the CER is reproduced below.

Figure 1: Kaplan-Meier plot of rate of clinically significant CMV infection in Trial P001 sourced from the TGA's first round CER



Number of Subjects at Risk			
Letermovir	325	270	212
Placebo	170	85	70

Source: Section 12.1.3, p65 of the CER.

6.14 The Kaplan-Meier plot showed an increase in clinically significant CMV infection from 6.8% at Week 14 to 18.9% at Week 24 for letermovir-treated patients, compared to an increase from 41.3% to 44.3% for placebo-treated patients. While the rate of infection is lower for letermovir-treated patients, the rate almost tripled between Week 14 and Week 24 post-transplant. The CER also requested that the sponsor discuss arguments for and against continuing prophylaxis for 6 months. In response to the CER, the TGA delegate noted the post-hoc analyses of the Full Analysis Set (FAS) population were performed to identify patients potentially at higher risk of CMV infection beyond week 14 post-transplant and who may benefit from prolonged prophylaxis with letermovir. The following factors were identified as being associated with an increased risk of reactivation:

- GVHD after randomisation and prior to clinically significant CMV infection
- Concomitant steroid use after randomisation and prior to clinically significant CMV infection

- Baseline risk for CMV reactivation.
- Negative donor CMV sero-status.

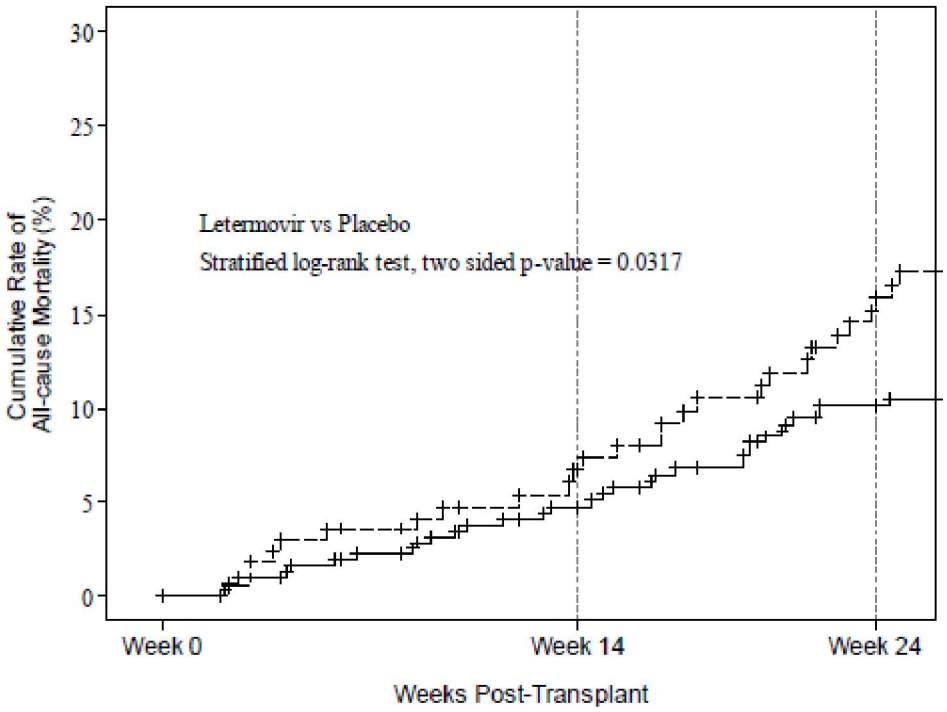
6.15 The ESC noted the argument raised in the PSCR and information provided the second round CER and TGA Delegate's overview. Whilst there is an increase in CMV infection post cessation of letermovir, there is still a reduction in overall incidence (less than half the incidence of placebo which is still statistically significant). There are also benefits to delaying CMV infection with increased risk of death of CMV infection within the first 60 days post-transplant (Green et al[3]). The ESC considered this to be both clinically plausible and expected as withdrawal of immunosuppression prior to day 100 is associated with a higher risk for early onset GVHD. The ESC agreed with the PSCR that with a delayed onset of CMV, there is a higher likelihood of the patients' immune system having recovered sufficiently to avoid the more severe outcomes of GVHD.

6.16 The ESC noted that there is currently no data to support prophylaxis for 6 months. The ESC noted that the sponsor informed the TGA of a planned study by the sponsor, P040, comparing efficacy outcomes in subjects treated with 100 days vs. 200 days of letermovir. Though this study is not yet registered on clinicaltrials.gov (as of 5 June 2018), the ESC considered that treatment duration in practice would evolve quickly as evidence becomes available. A longer treatment duration may reduce CMV infection until a time when most patients have robust immune reconstitution, although there is no evidence to support use for 6 months.

6.17 The Kaplan-Meier plots for time to all-cause mortality at Week 24 and Week 48, an exploratory outcome in Trial P001, are provided below.

[3] Green, M.L., et al., CMV Viral Load and Mortality after Hematopoietic Cell Transplantation: A Cohort Study in the Era of Preemptive Therapy. Lancet Haematology, 2016. **3**(3): p. e119-e127.

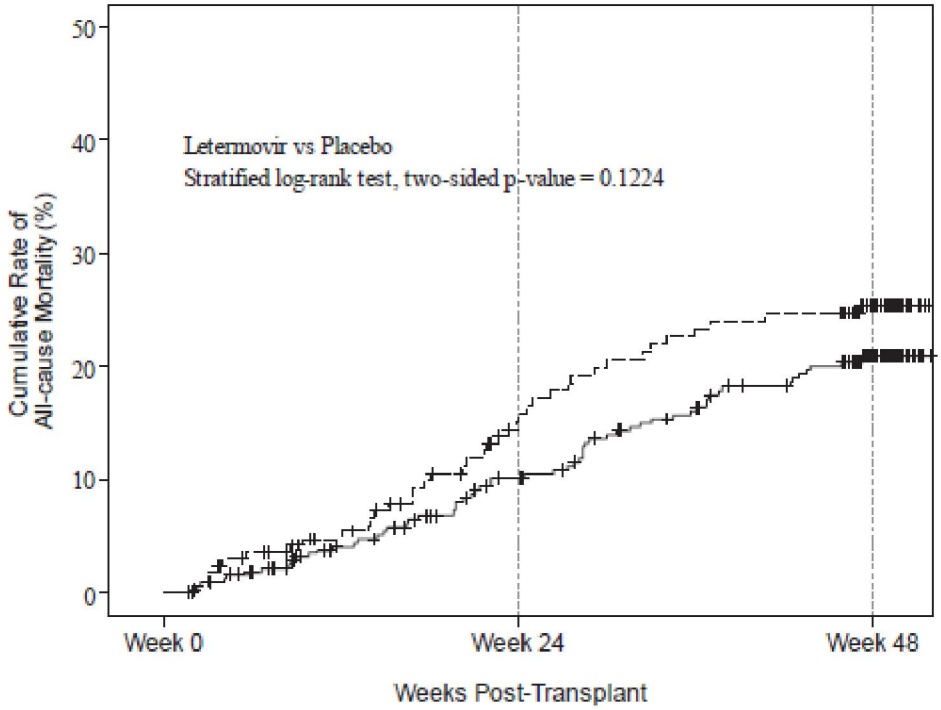
Figure 2: Kaplan-Meier plot of time to all-cause mortality through Week 24 post-transplant in Trial P001



No. at risk: KM estimates % (95% CI)			
Letermovir	325	290: 4.8 (2.4, 7.2)	262: 10.2 (6.8, 13.6)
Placebo	170	147: 6.7 (2.9, 10.5)	125: 15.9 (10.2, 21.6)

Source: Figure 2-4, p52 of the submission.

Figure 3: Kaplan-Meier plot of time to all-cause mortality through Week 48 post-transplant in Trial P001



No. at risk: KM estimates % (95% CI)			
Letermovir	325	262: 10.2 (6.8, 13.6)	138: 20.9 (16.2, 25.6)
Placebo	170	125: 15.9 (10.2, 21.6)	71: 25.5 (18.6, 32.5)

Source: Figure 2-5, p53 of the submission.

6.18 While there was a statistically significant advantage in all-cause mortality at Week 24 for letermovir, there was no statistically significant difference in all-cause mortality at Week 48.

6.19 At Week 24 the updated CSR for Trial P001 reported there was a statistically significant difference for the distribution of time to CMV-related mortality for letermovir (Kaplan-Meier event rate=0.7%) versus placebo (Kaplan-Meier event rate=9.1%) with a p value <0.0001 (the CSR provided with the submission stated the difference at 24 weeks was not statistically significant). The Week 48 CSR indicated that CMV-related mortality was identified as all-cause mortality in patients who met the primary endpoint of the trial (i.e. CMV infection), and this was statistically significantly different between letermovir (Kaplan-Meier event rate=3.6%) and placebo (Kaplan-Meier event rate=16.0%) with a p value <0.0001.

6.20 In regard to results for all-cause mortality at Week 48, the submission argued that the lack of a statistically significant difference was likely due to the trial not being statistically powered to detect a difference at 48 weeks. There was no discussion

regarding of the strength of the results showing a statistically significant advantage for letermovir at Week 48 for CMV related mortality. There is a discordance in mortality outcomes at Week 48, where all-cause mortality was not statistically significantly different between letermovir and placebo (p=0.1224) but CMV-related mortality showed a statistically significant difference between the two groups (p<0.0001). The PSCR reiterated that all-cause mortality was an exploratory endpoint in the trial and the trial was not powered to detect a statistically significant difference.

6.21 The submission provided a summary of change from baseline in EQ-5D index scores, EQ-5D VAS scores and FACT-BMT scores. These scores are reproduced in the table below.

Table 5: Change from baseline in patient-reported QoL outcomes in Trial P001

	Baseline		Week 14 post-transplant		Week 24 post-transplant		Week 48 post-transplant		All infection/ discontinuation visits	
	Leter	PBO	Leter	PBO	Leter	PBO	Leter	PBO	Leter	PBO
EQ-5D Index scores										
N										
Mean (SD)										
Mean change from baseline (SD)	-	-								
EQ-5D VAS scores										
N										
Mean (SD)										
Mean change from baseline (SD)	-	-								
FACT-BMT total scores										
N										
Mean (SD)										
Mean change from baseline (SD)	-	-								

EQ-5D=EuroQoL 5 Dimensions; FACT-BMT=Functional Assessment of Cancer Therapy – Bone Marrow Transplant; SD=standard deviation; VAS=visual analogue scale.
Source: Table 2-11, p55-56 of the submission.

6.22 No statistical comparisons of the QOL scores were provided in the Trial P001 CSR. The submission provided discussion of minimally important differences (MIDs) and stated that while MIDs have not been defined for the instruments used in the trial and in this specific population, studies in similar populations have suggested a MID of 0.06 to 0.08 for the EQ-5D Index, 0.07 for the EQ-5D VAS and 5 points for the FACT-BMT. The submission stated that the difference in mean change score from baseline between letermovir and placebo approached the published MID range for the EQ-5D Index, was under or around the lower end of the range for the FACT-BMT

and showed only small difference for the EQ-5D VAS. These conclusions should be interpreted with caution as the Trial P001 CSR had stated that the trial was not powered to detect minimal clinically important differences in health-related QoL scores between treatment groups and the QoL analyses were primarily descriptive and exploratory in nature.

6.23 The PSCR provided post-hoc statistical analyses of the QoL scores (the post baseline sample sizes have increased for these analyses versus those presented in the submission, and consequently the mean scores and mean change from baseline scores differ). The differences between the treatment groups were not statistically significant. The PSCR stated, the proportion of subjects who had a minimal important difference from baseline were generally higher in the letermovir group than in the placebo group, but there were no material differences between groups.

6.24 The submission provided, in an attachment to the submission, results of a number of sub-group analyses assessing the primary outcome by patient characteristics (e.g. age, gender), risk categories, and conditioning regimen and immunosuppressive regimens used (results are available in Attachment 2 of the commentary). The submission stated there was no evidence of treatment modification across all sub-groups. The sub-group analyses were based on the data as observed approach (any patient with missing data was excluded from analysis) instead of the non-completer=failure approach used for the whole trial population analyses. There was also an indication of treatment modification in the sub-groups based on mismatched unrelated donors.

6.25 The incidence of re-hospitalisation was presented in Table 6 (from p8 of Attachment 8 of the submission). The PSCR reiterated that treatment with letermovir was associated with reduced re-hospitalisations for CMV infection or disease; therefore the assumption that patients with CMV would be hospitalised is not unreasonable. The ESC considered this assumption to be uncertain given that there were overlapping confidence intervals for a number of data sets. In the economic model it was assumed that patients with CMV disease would be hospitalised and some patients with acute and chronic GVHD would be hospitalised. Results for GVHD are discussed as part of the 'Economic analysis' below.

Table 6: Proportion of subjects with re-hospitalisations after transplant through weeks 14, 24 and 48 post-transplant (FAS population)

	Letermovir (N = 325)			Placebo (N = 170)		
Response Variable	**n**	**M**	**% (95% CI)**	**n**	**m**	**% (95% CI)**
Through week 14 post-transplant						
All re-hospitalisations	118	168	36.3 (31.1, 41.8)	81	107	47.6 (39.9, 55.4)
Re-hospitalizations for CMV infection/disease	2	2	0.6 (0.1, 2.2)	12	12	7.1 (3.7, 12.0)
Through week 24 post-transplant						
All re-hospitalisations	158	278	48.6 (43.1, 54.2)	94	146	55.3 (47.5, 62.9)
Re-hospitalizations for CMV infection/disease	10	11	3.1 (1.5, 5.6)	13	13	7.6 (4.1, 12.7)
Through week 48 post-transplant						
All re-hospitalisations	181	354	55.7 (50.1, 61.2)	103	183	50.6 (52.8, 68.0)
Re-hospitalizations for CMV infection/disease	10	11	3.1 (1.5, 5.6)	15	16	8.8 (5.0, 14.1)

N = number of evaluable subjects in in each treatment group.
n = Number of subjects in each sub-category.
m = Number of unique episodes in each sub-category.
% = Percent of subjects in each sub-category.
Source: Table 8 of Attachment 8 of the submission.

6.26 A phase II trial comparing letermovir and placebo for prophylaxis of CMV infection following allogeneic HSCT was published by Chemaly (2014). This was a randomised, double-blind trial comparing three doses of letermovir, 60mg/day, 120mg/day and 240mg/day. Following 12 weeks of treatment the results indicated that the 240mg/day dose had the highest anti-CMV activity. While the 240mg/day dose corresponds to the dose used in Trial P001 in combination with cyclosporin, there was no indication that cyclosporin was used concomitantly with letermovir in the Phase II trial. This phase II trial did not include a dose of 480mg/day, which was given in Trial P001.

Comparative harms

6.27 A summary of safety results from Trial P001 is provided in the table below. These results were provided for the overall ITT trial population, i.e. including patients with CMV DNA on Day 1 who were excluded from effectiveness analyses. As such, this population differed from the population upon which analysis of the primary outcome was based, as it excluded patients for whom CMV DNA was detected on Day 1 of treatment.

Table 7: Summary of safety results in the Week 48 population post-transplant in Trial P001

Adverse event	Letermovir N=373 n (%)	Placebo N=192 n (%)	Difference (95% CI)	RR/OR[a] (95%CI)
Overall AEs				
With one or more AE	367 (98.4%)	192 (100%)	-1.6 (-3.5, 0.4)	0.22 (0.05, 0.94)[b]
With drug-related AEs	63 (16.9%)	25 (13.0%)	3.9 (-2.6, 9.7)	1.30 (0.84, 1.99)
With serious drug-related AEs	3 (0.8%)	3 (1.6%)	NA	0.49 (0.09, 2.66)
Discontinued due to drug-related AE	18 (4.8%)	7 (3.6%)	1.2 (-2.9, 4.5)	
Discontinued due to serious drug-related AE	3 (0.8%)	3 (1.6%)	NA	
Drug-related AEs				
Diarrhoea	[redacted]	[redacted]	[redacted]	
Nausea	[redacted]	[redacted]	[redacted]	
Vomiting	[redacted]	[redacted]	[redacted]	

a odds ratio was used instead of relative risk if incidence was ≤1% or ≥99% in at least one cell.
b Based on 365 events for letermovir arm. Difference in number of events not explained in PSCR.
AE=adverse event; CI=confidence interval; NA=not applicable; OR=odds ratio; RR=relative risk
Source: Table 2-13, p57 and Table 2-15, p59 of the submission.

6.28 The submission presented the differences in adverse event (AE) and 95% CIs as provided in the Week 48 CSR. The submission concluded the incidence of drug-related AEs with letermovir was comparable to that in the placebo group. This was reasonable for overall events. Gastrointestinal (GI)-related events such as nausea, diarrhoea and vomiting occurred at a rate in the letermovir group that, while relatively low, was numerically double that in the placebo group (see table above). Given the GI-related events are common in this patient group, the ESC considered it was difficult to draw conclusions on the outcomes of the trial.

6.29 Overall, there appeared to have been similar occurrence of AEs between letermovir and placebo. The TGA's first round CER concluded that while there was an increased risk of nausea, vomiting and diarrhoea with letermovir, these AEs were generally mild to moderate in severity and only had a modest increase in incidence compared to placebo. The ESC noted the statistical information provided in PSCR , and was of the view that it was reasonable to consider that adverse events reported in the submission are comparable between the arms of the trial.

6.30 There were also AEs that occurred in more letermovir-treated patients than placebo-treated patients that while not discussed in the submission were raised in the publication of Trial P001 (Marty 2017), specifically atrial fibrillation (3.5% of letermovir-treated patients vs 1.0% of placebo-treated patients) and atrial flutter (1.1% vs 0.0% in placebo). The Marty (2017) paper concluded (p2443) that while these events were rarely serious, they would require further evaluation in future studies. The ESC considered that these cardiac-related events should be part of the assessment of comparative safety. These events could potentially be serious, particularly in high risk patients with metabolic disturbances and with magnesium and potassium issues. The Pre-PBAC response argued that:

- No subject in the letermovir group experienced a drug-related cardiac-related adverse event.

- The TGA Delegate's Overview concluded that "the majority of these events were non-serious, of mild to moderate severity and confounded by concomitant use of known cardiotoxic medications, cardiac history and acute infections and possible imbalance in the proportion of subjects with baseline cardiac conditions between the letermovir and placebo arm".
- The first round Clinical Evaluator's Report also discussed the incidence of the cardiac adverse events, concluding that overall no specific safety concerns have been identified.

Benefits/harms

6.31 A summary of the comparative benefits for letermovir versus placebo is presented in the table below.

Table 8: Summary of comparative benefits for letermovir and placebo-treated patients based on Trial P001

Trial	Letermovir n/N (%)	Placebo n/N (%)	Stratum-adjusted treatment difference (95% CI)	Event rate/100 patients*	
				Letermovir	Placebo
Benefits - clinically significant CMV infection by Week 24					
Trial P001	122/325 (37.5%)	103/170 (60.6%)	**-23.5 (-32.5, -14.6)**	37.5	60.6

* Duration of follow-up: Trial P100=24 weeks for assessment of primary outcome.
CI=confidence interval
Source: Table 2-9, p49 of the submission.

6.32 On the basis of direct evidence presented by the submission and related publications, for every 100 patients treated with letermovir in comparison to placebo and over a duration of follow-up of 24 weeks:

- Approximately 23 fewer patients would have clinically significant CMV infection (a composite outcome including (i) onset of CMV end-organ disease and (ii) initiation of pre-emptive therapy).

6.33 As the comparison for safety outcomes did not indicate any statistically significant differences between letermovir and placebo, comparative harms are not presented. The ESC considered in the context of the timing post transplantation, the adverse events are relatively minor except for the potentially serious cardiac effects (discussed above).

Clinical claim

6.34 The submission described letermovir as superior in terms of effectiveness and non-inferior in terms of safety compared to placebo. While the therapeutic conclusion presented in the submission was supported by the statistically significant advantage of letermovir in prevention of CMV infection in CMV sero-positive patients who were recipients of an HSCT, there are a number of concerns with the evidence presented by the submission. The submission presented a list of what was demonstrated by

Trial P001; the concerns noted during the evaluation with the evidence are described below.

6.35 The submission stated that prophylaxis with letermovir has demonstrated:

- Significantly reduced incidence of CMV infection and as such, significantly reduced utilisation of other antivirals for PET. While the results of Trial P001 showed a statistically significant advantage for letermovir compared to placebo for incidence of CMV infection, there was no direct evidence of a decrease in use of other antivirals for PET. Instead, this was an assumption on the part of the submission. PET is used when an increase in viral load is detected in the absence of evidence of clinical disease. The ESC noted a reduction in CMV infection would be expected to result in a reduction in the use of PET.
- Improved overall survival, with lower all-cause mortality in the letermovir group compared to the placebo group through weeks 24 and 48 post-transplant. The main body of the submission only reported all-cause mortality and while the analyses showed a significant advantage for letermovir at Week 24, the advantage at Week 48 was not statistically significant. CMV-related mortality, was statistically significant different between letermovir and placebo-treated patients at Week 24 and at Week 48 ($P<0.0001$) (corrected week 24 results provided in PSCR). In regard to all-cause mortality at Week 48, the submission and PSCR argued that the lack of a statistically significant difference in all-cause mortality at Week 48 was likely due to the trial not being powered to detect a difference at 48 weeks. The ESC noted that the claim of superior all-cause mortality at 48 weeks was not supported by the data.
- Improved quality of life for patients treated with letermovir compared to placebo. There were no statistical analyses provided which compared QoL results and the Trial P001 CER stated that the trial was not powered to detect differences in QoL outcomes. The PSCR provided post-hoc statistical analyses of the QoL scores, discussed above in Clinical effectiveness. The changes from baseline in QoL scores were similar across groups, and in at least one instance were greater for placebo-treated patients. As such, the magnitude of change in quality of life outcomes for letermovir-treated patients could not be quantified. The ESC noted that there was no difference in quality of life in the trial, although it considered that it may have been difficult to detect a difference, as the trial covered the period of time when patients are in poor health recovering from the transplant. The ESC noted this was somewhat at odds with the trial-based utility values which appear to be implausibly high, given how unwell post-transplant patients are likely to be.
- Fewer hospitalisations related to CMV infection and/or disease compared to the placebo group through Week 48 post-transplant. In the economic model (see 'Economic analysis' below for further discussion) the submission assumed that patients with CMV disease and acute and chronic GVHD would be hospitalised. Patients were not hospitalised for CMV infection in the model and there was only a small proportion of patients experiencing CMV disease. Most hospitalisation in

the economic model was based on the occurrence of GVHD. As discussed above, the ESC noted the extent of reduction in hospitalisations was uncertain.

- Favourable safety profile, with letermovir demonstrating a safety profile which was similar to and arguably more favourable than placebo, due to reduced utilisation of antivirals for PET in the letermovir group. While the occurrence of AEs was comparable across the letermovir and placebo groups, the submission did not link the occurrence of AEs, or lack thereof, with antiviral use. As such, the claim made by the submission that the favourable safety profile of letermovir is due to reduced use of antivirals cannot be supported. The ESC noted the impact of reduced antiviral use on safety outcomes was not clear.

6.36 The outcomes from Trial P001 that were used in the economic model were: CMV infection, CMV disease, occurrence of GVHD (Grade II and Grade III-IV) and all-cause mortality. Quality of life outcomes (EQ-5D) were not applied as literature-based utility values were used. The ESC noted that the submission and the PSCR did not provide an explanation for why trial-based utilities were not used.

For more detail on PBAC's view, see section 7 PBAC outcome.

Economic analysis

6.37 The submission presented a stepped economic evaluation, based on Trial P001 with extrapolation of mortality data. A seven health state Markov model was used, and the type of economic evaluation presented was a cost-utility analysis. The key components of the economic evaluation are summarised in the table below.

Table 9: Summary of model structure and rationale

Component	Summary
Time horizon	10 years in the model base case versus 48 weeks in Trial P001.
Outcomes	Life years gained (LYG) and quality-adjusted life years (QALYs)
Methods used to generate results	Markov model
Health states	7 health states: post-transplant; CMV infection; CMV disease; acute GVHD Grade II, acute GVHD Grade III-IV, chronic GVHD, death
Cycle length	1 week
Transition probabilities	Trial P001
Utility values	Literature based

Source: Table 3.1, p67 of the submission.

6.38 A summary of the key drivers of the economic model is provided in the table below.

Table 10: Key drivers of the model

Description	Method/Value	Impact
Extrapolation	The submission applied extrapolation of mortality data from Week 1 to 10 years. Model results showed that over 80% of placebo-treated patients were dead at 5 years, and approximately 50% were dead at 3 years. Given most deaths following HSCT occur within 2 years and for patients alive at 2 years, survival at 10 years is approximately 85% (Wingard 2011), such extrapolation does not accurately represent the proposed PBS population.	High, favours letermovir
Utilities	Literature-based values sourced from populations not representative of the proposed PBS population were used when there were trial-based EQ-5D values available. (The submission did not provide an explanation to why trial-based values were not considered for use in the economic model). The values for post-transplant and CMV infection (both 0.9) seemed high for patients that are considerably unwell.	High, favours letermovir
GVHD	There were no statistically significant differences in the occurrence of GVHD for letermovir and placebo-treated patients in Trial P001 and between-group differences are very small, e.g. 17.5% of letermovir-treated patients and [redacted]% of placebo-treated patients reported Grade II GVHD. The ICER almost doubled, to over $45,000/QALY when the same probabilities for GVHD are used for letermovir and placebo.	High, favours letermovir

Source: Compiled from Section 3 of the submission during the evaluation.

6.39 The results of the economic evaluation are provided in the table below.

Table 11: Results of the stepped economic evaluation

Step and component	Letermovir	Placebo	Increment
Step 1: trial-based costs and outcomes			
Costs	$[redacted]	$0	[redacted]
Proportion with clinically significant CMV infection	37.5%	60.6%	23.1%
Incremental cost/clinically significant CMV infection avoided			$[redacted]
Step 2: Model duration to 10 years with all event costs included and life years applied			
Costs	$[redacted]	$[redacted]	$[redacted]
LYG	3.29	2.72	0.58
Incremental cost/extra LYG gained			$[redacted]
Step 3: Utility weights included			
Costs	$[redacted]	$[redacted]	$[redacted]
QALY	2.84	2.31	0.53
Incremental cost/extra QALY gained (base case)			**$[redacted]**

Source: Table 3-13, p95 of the submission.

6.40 The cost per clinically significant CMV infection avoided in Step 1 of the model was $75,000 - $105,000. The cost/QALY gained (step 3) was marginally higher than the cost/LY gained (step 2). While the PSCR discussed the rate of CMV infection between Week 14 and Week 24, the ESC was uncertain if these changes in rate of CMV were appropriately included in the modelling.

6.41 The base case ICER of $15,000/QALY - $45,000/QALY was not likely to accurately represent the cost-effectiveness of letermovir. With over 70% of letermovir patients and over 80% of placebo patients dead at around 5 years, the mortality extrapolation applied in the model does not reflect the survival expected for the

proposed PBS population, where the literature indicates that for patients who survive to two years, approximately 85% are alive at 10 years (Wingard 2011). It may have been appropriate for the submission to apply available two year survival data (Week 48 data from Trial P001 and ABMTRR data to 2 years) followed by extrapolation to 10 years, instead of extrapolation from Week 1. The ESC agreed with the evaluation, noting the argument raised in the PSCR. The ESC noted that the 10 year survival data in the ABMTRR annual report 2016 broadly supported the conclusions of Wingard 2011. The ESC considered that it is likely that if a patient is alive at 2 years post HSCT, they have a high likelihood of long term survival.

6.42 In addition, a number of inputs to the model are not likely to be representative of those seen in clinical practice, in particular the utility values used, along with the costs applied for GVHD. Decreasing the post-HSCT transplant utility value of 0.9 by 20% to 0.72 (corresponding to the change in utility value applied by the submission for GVHD utility values) increased the ICER to $15,000/QALY - $45,000/QALY. The PSCR reiterated utility values used for the HSCT post-transplant state (0.9) represent patient without chronic GVHD. The ESC noted this, but reiterated its concern about the seemingly implausibly high values for some health states, that modelled unwell patients. It was further noted that neither the submission nor PSCR provided an explanation to why trial-based values were not considered for use in the economic model, although, as noted in the clinical issues above, the values sourced from the trial also appeared high.

6.43 Inclusion of three health states for GVHD (acute GVHD Grade II, acute GVHD Grade III-IV and chronic GVHD) seemed unnecessary given there was no statistically significant difference in the occurrence of GVHD in Trial P001. A sensitivity analysis making the occurrence of GVHD the same between letermovir and placebo increased the ICER to over $45,000/QALY - $75,000/QALY. The PSCR argued as GVHD is associated with a significant impact on both health outcomes and health care resources utilisation, it is important to capture these long-term impacts in the model. The ESC acknowledged that avoidance of GVHD is a patient-relative outcome. However, the ESC considered that need for splitting GVHD into multiple health states has still not been addressed.

6.44 The economic model assumed that [redacted]% of patients would use concomitant cyclosporin and therefore the 240mg/day dose of letermovir. The ESC noted that cyclosporin is generally used as standard practice in clinics and considered that the assumption was reasonable. The ESC noted that the submission considered that uncertainty around the rate of cyclosporin use, as well as treatment duration, could be addressed through a risk sharing arrangement. The ESC noted that if the duration of cyclosporin treatment does not match letermovir treatment, then a patient may be require to increase the dose of letermovir to 480 mg/day. In its financial estimates, the submission applied a sensitivity analysis assuming use of cyclosporin in 80% of patients. When the same value was applied to the costing of letermovir in the economic model, the ICER increased to $15,000/QALY - $45,000/QALY.

6.45 The economic model also assumed that patients would only be treated for 78 days, as in Trial P001, however the requested restriction provides 112 days of treatment (greater than the 100 days of recommended treatment). The mean treatment duration for oral letermovir was [redacted] days (Updated Week 24 CSR, provided with PSCR). The ESC considered that in practice nearly all patients will be treated for a period longer than 78 days. As discussed above in the Comparative effectiveness Section, the treatment duration in practice would evolve quickly; therefore the ESC considered that the likely duration of therapy in clinical practice (and cost) remains unclear. When cost for 112 days of letermovir treatment was included in the model, the ICER increased to $15,000/QALY - $45,000/QALY. With both the longer treatment duration (112 days) and use of cyclosporin in 80% of patients, the ICER increased to $45,000/QALY - $75,000/QALY.

6.46 The model demonstrated considerable sensitivity to duration, with a time horizon of 2 years resulting in an ICER of $105,000/QALY - $200,000/QALY compared to $15,000/QALY - $45,000/QALY at 10 years in the base case. When coupled with the fact that virtually all events (CMV infection, CMV disease, GVHD) occurred within the first year of the model, the impact of the extrapolation applied suggested that the model was not likely to have accurately estimated the cost-effectiveness of letermovir. The PSCR argued that the 10-year time horizon is justified due to the long-term implications of CMV infections and GVHD after HSCT, in terms of increased mortality and reduced quality of life. The ESC noted that a 10 year time horizon may be reasonable to capture the life years gained (LYG) from deaths avoided due to CMV infections but that the results using this time horizon were not reliable because the extrapolations applied in the submission were implausible.

6.47 The PSCR stated the sponsor acknowledges uncertainty regarding long-term mortality and analyses were presented using trial data up to 42 weeks followed by lognormal extrapolation as well as trial data followed by natural mortality using Australian life expectancy tables. The results of these analyses for both 5 and 10 year model durations are provided in the table below. The ESC noted that it was not possible to verify the ICERs using different approaches and datasets for extrapolations as part of the response process; however the additional analyses confirmed the sensitivity of the model to the time horizon and the extrapolation approach.

Table 12: Analyses with mortality extrapolation altered from the submission's base case

Step and component	Letermovir	Placebo	Increment
Submission base case – 10 year time horizon			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
QALY	2.84	2.31	0.53
Incremental cost/extra QALY gained			**$ [redacted]**
Scenario 1: trial data at 48 weeks and log-normal extrapolation with a 10 year time horizon			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
QALY	4.31	4.01	0.30
Incremental cost/extra QALY gained			$ [redacted]
Scenario 2: trial data at 48 weeks and natural mortality with a 10 year time horizon			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
QALY	4.78	4.47	0.31
Incremental cost/extra QALY gained			$ [redacted]
Submission sensitivity analysis – 5 year time horizon			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
QALY	2.30	1.99	0.31
Incremental cost/extra QALY gained			$ [redacted]
Scenario 3: trial data at 48 weeks and log-normal extrapolation with a 5 year time horizon			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
QALY	2.73	2.54	0.19
Incremental cost/extra QALY gained			$ [redacted]
Scenario 4: trial data at 48 weeks and natural mortality with a 5 year time horizon			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
QALY	3.00	2.81	0.19
Incremental cost/extra QALY gained			$ [redacted]

Source: Table 3, p8 of the PSCR; Table 3-16, p97 and Table 3-17, p99 of the submission.

The redacted table shows ICERs in the range of $15,000/QALY - $75,000/QALY.

6.48 Overall, the ESC had considerable concerns about the validity of the model and considered that it was unlikely to provide an accurate estimation of the cost-effectiveness of letermovir.

For more detail on PBAC's view, see section 7 PBAC outcome.

Drug cost/patient/course

6.49 The submission provided the drug cost for letermovir over the 78 day duration of treatment in the economic model ($[redacted] per patient). Given that the duration of treatment in the economic model was based on Trial P001, and the drug cost assumed [redacted]% of patients would use the 240mg/day dose, this cost is not likely to reflect the cost of letermovir in clinical practice. The recommended treatment duration is 100 days, and the requested restriction provides for 112 days of treatment. Given these factors, letermovir treatment costs have been calculated for both 100 and 112 days of treatment for both the 240mg/day and 480mg/day doses. The cost assuming [redacted]% using 240mg/day and [redacted]% using 480mg/day has also been calculated for the 100 and 112 day durations. These costs are provided in the table below.

Table 13: Letermovir treatment cost

Dose	Cost/day ($ /pack)	Treatment duration	Total cost
240mg/day	$	100 days – recommended treatment	$
		112 days – as provided under the requested restriction	$
480mg/day	$	100 days – recommended treatment	$
		112 days – as provided under the requested restriction	$
% using 240mg/day and % using 480mg/day	$	100 days – recommended treatment	$
		112 days – as provided under the requested restriction	$
Sensitivity Analysis: 80% using 240mg/day and 20% using 480mg/day	$ [a]	100 days – recommended treatment	$
		112 days – as provided under the requested restriction	$
As presented by the submission			
% using 240mg/day and % using 480mg/day	$	78 days – as used in the model	$

Source: Section 3.8.1 of the submission and requested price of letermovir. The price of $ daily was calculated using the following formula (x) + (x (x2)). On page 88 of the submission, the formula incorrectly was written as (x (x2)).

[a] Formula used was (0.8x) + (0.2x (x2))

6.50 Using the two available doses, either alone or in the proportion based on ABMTRR data, the cost for treatment as provided under the requested restriction (112 days) will range from just over $ to just over $.

Estimated PBS usage & financial implications

6.51 This submission was considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial implications associated with PBS listing of letermovir for the prophylaxis of CMV infection in patients who have received or are receiving an allogeneic HSCT. The submission used Australian Institute of Health and Welfare (AIHW) data to estimate the number of allogeneic bone marrow or stem cell transplants, along with use of Australasian Bone Marrow Transplant Recipient Registry (ABMTRR) data to identify adult patients; seropositive patients; and patients using cyclosporin to estimate use of letermovir.

6.52 The submission provided estimates for only 5 years, instead of the 6 years recommended in the PBAC Guidelines (v5.0, Section 4.2*).* The estimated number of patients, scripts and estimated net cost to the PBS/RPBS are provided in the table below. The PSCR updated the expected cost to include Year 6 of listing. The net cost to PBS/RPBS in Year 6 was estimated to be less than $10 million.

Table 14: Estimated number of letermovir scripts in the first 5 years of listing

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of letermovir					
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Co-payments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to PBS/RPBS	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]

[a] Assuming a weighted average of 3.21 packs per year ([redacted]% using concomitant cyclosporin and 240mg/day and [redacted]% using letermovir alone and 480mg/day).

Source: Table 4-5, p109-110; Table 4-8, p111; Table 4-9, p112 of the submission.

6.53 The submission estimated patient numbers of less than 10,000 per year, and estimated net costs totalled $30 - $60 million over the first 6 years of listing.

6.54 Overall, DUSC considered the estimates presented in the submission to be underestimated, because:

- The proposed PBS restriction permits use in a broader population than the eligible population determined in the financial estimates. In particular, age, timing of CMV serostatus testing and maximum duration of therapy were not specified in the requested restriction (as discussed in Section 2 Requested Listing).
- There is uncertainty regarding the duration of treatment. The median treatment duration in the clinical trial (78 days), which was used in the financial estimates, is considerably less than the 100 days of recommended duration, and the 112 days of treatment that would be available to patients based on the requested restriction.. The PSCR stated that it would be unreasonable to expect that all patients will receive the full amount of 112 tablets on the PBS. However, DUSC considered that the duration of treatment is still uncertain. DUSC also noted the potential for letermovir to be used for a longer period of time in some patients due to the potential for rebound viraemia.
- The submission's financial estimates were based on the assumption that [redacted]% of patients would be on cyclosporin (from current Australian practice rather than the 52% from the clinical trial) and therefore only require the lower dose of letermovir. In the PSCR, the sponsor maintained that the ABMTRR data represents ideal real-world utilisation data to estimate utilisation of cyclosporin in this patient population and there are no known reasons to anticipate a change in clinical practice as cyclosporin has been available for many years. The submission acknowledged that uncertainty around this rate of cyclosporin use, as well as treatment duration, could be addressed through a risk sharing arrangement. DUSC agreed with the commentary regarding the uncertainty of whether the rate of cyclosporin use has been stable and will continue to remain the same in the future.

6.55 Given that a treatment duration based on the number of packs available with the requested restriction is more likely to apply in practice (112 days, therefore including wastage), this change has been combined with a change in proportion of patients using cyclosporin (i.e. the 240mg/day dose; decrease to 80% from [redacted]% in the base case). This sensitivity analysis increased estimated net cost over the first 5 years of listing to a total of $60 - $100 million compared with the $30 - $60 million estimated in the submission's base case.

6.56 The Pre-PBAC response stated any uncertainty in the real world utilisation of letermovir will be addressed with a risk sharing arrangement between the sponsor and the government, such that the impact of extended duration outside of the proposed estimates does not have a significant impact to the health budget. However, the sponsor reiterates that the use of the median trial duration is reasonable to estimate real-world utilisation of letermovir. There are a number of clinical reasons to delay starting letermovir or cease letermovir before day 100 post-transplant. It is for these reasons that the median duration of treatment in the trial was observed as 78 days. It is therefore not reasonable to expect that all patients will receive the maximum amount of letermovir.

For more detail on PBAC's view, see section 7 PBAC outcome.

Quality Use of Medicines

6.57 The submission provided a list of proposed activities to support the quality use of medicines, including development of materials to be provided to physicians, nurses, pharmacists and patients; educational activities; and development of materials to support responses to requests for information on the sponsor's 1800 medical information service number.

6.58 The submission added that no additional post-market surveillance studies or risk minimisation activities are currently proposed for letermovir.

6.59 DUSC highlighted that educational materials and activities on drug interactions would be crucial to support appropriate use of letermovir. There are significant drug interactions associated with co-administration of letermovir (as it is a CYP3A inhibitor and an OATP1B1/3 substrate) and the magnitude of the interactions may have been understated by the submission, as lower doses of letermovir were used in the drug-drug interaction studies compared with the requested listing.

6.60 DUSC reiterated that the draft PI did not mention cessation of therapy when patients develop CMV infection.

Financial Management – Risk Sharing Arrangements

6.61 The submission stated that treatment duration and proportion of patients using cyclosporin may impact the net cost to the PBS and the sponsor is willing to enter a risk sharing arrangement with a cap/rebate structure that takes into account this

uncertainty. The submission added that the sponsor believes the risks should be shared with the Commonwealth and that any rebate payable should not exceed 50%, as elements of the uncertainty being addressed are outside the control of the sponsor and are not able to be forecasted. The submission indicated that final details of the risk sharing arrangement would be negotiated with the Department of Health following a positive PBAC recommendation.

7 PBAC Outcome

7.1 The PBAC did not recommend the Section 100 (Highly Specialised Drugs Program) Authority Required listing for letermovir for prophylaxis of cytomegalovirus (CMV) infection or disease in CMV sero-positive patients who have received an allogeneic haematopoietic stem cell transplant (HSCT). This decision was on the basis that the Committee was unable to assess the cost-effectiveness of letermovir treatment because the economic analysis did not appropriately model the health benefits of treatment as demonstrated in the clinical trial.

7.2 The PBAC noted the consumer comments and acknowledged the clinical utility of an orally active agent to prevent CMV infection and that letermovir was less toxic than existing antiviral agents.

7.3 The PBAC noted the Secretariat and Sub-Committee feedback on the restriction proposed in the submission, which was agreed by the sponsor in the Pre-PBAC response. While noting other PBS-listed antiviral treatments include a PBS indication of 'Cytomegalovirus infection and disease' and 'Treatment Phase: Prophylaxis', the PBAC considered that for letermovir it would be clearer for the PBS indication to be 'Prophylaxis of cytomegalovirus infection and disease'. The PBAC noted that the proposed pack size, maximum quantity and number of repeats (112 tablets) would result in wastage compared to the treatment of 100 days as per the current product information. As highlighted by the clinician at the Sponsor hearing, patients undergoing a HSCT are regularly monitored by experienced clinical teams, and thus the PBAC considered that it was not necessary to include criteria for when to measure antibodies, or related to not starting or not using letermovir in the presence of CMV infection. The PBAC agreed with DUSC that the restriction should include reference to the time period when treatment commences, for example 'Treatment must commence within 28 days of an allogeneic haematopoietic stem cell transplant'.

7.4 The PBAC noted the sponsor's argument that placebo should be the main comparator as the majority of patients in Australia do not receive prophylaxis for CMV infection following HSCT. The submission argued that patients who receive letermovir and develop CMV infection would still receive PET to treat an active infection. The PBAC noted the evidence, such as the ABMTRR report, showed that antiviral treatments are used in Australian practice, either prophylactically or as PET, and their use would likely reduced with the availability of letermovir. The PBAC considered that both placebo and antiviral treatments would be informative

comparators.

7.5 The PBAC noted that the clinical evidence presented in the submission was based on Trial P001. The PBAC noted the primary outcome in Trial P001, the proportion of patients with clinically significant CMV infection at Week 24, was a composite outcome including (i) onset of CMV end-organ disease and (ii) initiation of pre-emptive therapy (PET) based on documented CMV viraemia and the clinical condition of the patient. The PBAC noted compared with placebo, letermovir treatment decreased the incidence of CMV infection and that this was due to a difference in the proportion of patients requiring PET (40.0% versus 16.0%) but not the proportion with CMV end-organ disease (1.8% versus 1.5%). The PBAC noted letermovir treatment had not been demonstrated to reduce the incidence of GVHD (39.1% of patient in the letermovir treatment group versus 38.5% in the placebo group; p=0.96) or all-cause mortality (p=0.12). Overall, the PBAC considered that it had been demonstrated that letermovir reduces the use of PET but there was little or no difference in CMV disease and associated sequalae.

7.6 Further, the PBAC noted the recent meta-analysis of comparative efficacy and safety of different antiviral agents for CMV prophylaxis in allogeneic HSCT, which included letermovir[4]. While the publication concluded across the network, ganciclovir showed the best relative efficacy for CMV disease while letermovir was ranked at being the best option for CMV infection, the PBAC noted that overall the analysis suggested that there was probably little or no difference in the effect of letermovir in preventing CMV disease compared with other antivirals.

7.7 The PBAC considered that a claim of non-inferior safety compared to placebo (the submission's nominated comparator) was appropriate, agreeing with ESC that it was reasonable to conclude that adverse events reported in the submission were comparable between the arms of the trial. In regards to atrial fibrillation and atrial flutter, the PBAC noted that the Marty (2017) paper concluded that while these events were rarely serious (which was also the current view of the TGA when registering the agent), they would require further evaluation in future studies. The PBAC also noted the submission's claim of more favourable safety compared with placebo due to reduced utilisation of antivirals for PET. The PBAC acknowledged that there are well known toxicities (e.g. bone marrow suppression) associated with currently used antiviral treatments.

7.8 The PBAC shared the concerns of ESC and considered that the economic analysis did not provide an accurate estimation of the cost-effectiveness of letermovir. The PBAC noted the issues raised by the ESC, including that the outcomes driving the economic model (the occurrence of GVHD and all-cause mortality) were not significantly

[4] Gagelmann N et al, Comparative Efficacy and Safety of Different Antiviral Agents for Cytomegalovirus Prophylaxis in Allogeneic Hematopoietic Cell Transplantation: A Systematic Review and Meta-Analysis. Biol Blood Marrow Transplant. 2018 May 16. pii: S1083-8791(18)30269-6.

different in the trial. The PBAC considered that the model should be based on the health benefits demonstrated in the trial, i.e. a reduction in the use of PET.

7.9 The PBAC noted the view of DUSC that the estimates of utilisation presented in the submission are underestimated. As with the economic analysis, the driver of the assumed cost of treatment was the duration of treatment and the rate of patients using the lower amount of letermovir with concomitant cyclosporin. The PBAC considered that, as raised by the ESC, cyclosporin is generally used as standard clinical practice, however considered further evidence to show historical long term trends in cyclosporin use in HSCT to address uncertainty of the assumption of [redacted]% of usage in Australian patients.

7.10 The PBAC considered that a resubmission would need to be in the form of a major submission and should be based on the effects of letermovir treatment as demonstrated by the clinical evidence, that is a reduction in the use of PET and associated health gains due to avoidance of side effects associated with PET.

7.11 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

The sponsor is disappointed with the PBAC outcome and is committed to working with the government to ensure PREVYMIS is made available as soon as possible to all patients undergoing allogeneic bone marrow transplants who are at risk of CMV reactivation and its associated poor outcomes.