

## 7.08 LETERMOVIR, Tablet 240 mg, Prevymis™, Merck Sharpe & Dohme (Australia) Pty Ltd

### 1 Purpose of Application

- 1.1 The resubmission requested a Section 100 (Highly Specialised Drugs Program) Authority Required listing for letermovir for prophylaxis of cytomegalovirus (CMV) infection or disease in CMV seropositive patients who have received an allogeneic haematopoietic stem cell transplant (HSCT). The first submission was in July 2018.
- 1.2 As for the July 2018 submission only the 240mg tablets are proposed for listing. The sponsor has indicated reimbursement is not being sought for the IV formulation although the IV formulation will be made available for use in a hospital setting.
- 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 resubmission are presented in Table 1.

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

| Component      | Description   |
|----------------|---|
| Population     | Adult CMV-seropositive recipients [R+] of an allogeneic HSCT.   |
| Intervention   | Letermovir 240mg IV/oral per day when used concomitantly with cyclosporin (or 480mg IV/oral daily if used alone) through 100 days post-transplant in addition to standard of care pre-emptive treatment for active CMV infection as required. |
| Comparator     | Placebo prophylaxis in addition to standard of care pre-emptive treatment for active CMV infection as required.   |
| Outcomes       | Clinically significant CMV infection and survival.  |
| Clinical claim | Letermovir is superior in terms of efficacy and has non-inferior safety in the prophylaxis of CMV infection or disease compared to placebo.   |

Source: Table 1-2, p5 of the resubmission.

### 2 Requested listing

- 2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

| Name, Restriction, Manner of administration and form | Max. Qty (packs)  | No. of Rpts | Dispensed Price for Max. Qty | Proprietary Name and Manufacturer                  |
|--|---|-------------|------------------------------|--|
| Letermovir 240 mg tablet, 28                         | 1   | 3           | \$ [REDACTED]                | Prevymis™ Merck Sharpe & Dohme (Australia) Pty Ltd |
| <b>Category/Program</b>                              | Section 100 – <del>Authority Required</del> Highly Specialised Drugs Program (Private and Public Hospitals)   |             |                              |  |
| <b>Prescriber type:</b>                              | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists<br><input type="checkbox"/> Midwives |             |                              |  |
| <b>Episodicity:</b>                                  | N/A Prophylaxis   |             |                              |  |
| <b>Severity:</b>                                     | N/A   |             |                              |  |
| <b>Condition:</b>                                    | Cytomegalovirus infection and disease   |             |                              |  |

Public Summary Document – March 2019 PBAC Meeting

|                                    |  |
|------------------------------------|--|
| <b>PBS Indication:</b>             | Prophylaxis of cytomegalovirus infection and disease   |
| <b>Treatment phase:</b>            | Prophylaxis  |
| <b>Restriction Level / Method:</b> | <input type="checkbox"/> Restricted benefit<br><input checked="" type="checkbox"/> Authority Required - In Writing (Public/Private)<br><input checked="" type="checkbox"/> Authority Required – Telephone (Public/Private)<br><input type="checkbox"/> Authority Required – Emergency<br><input type="checkbox"/> Authority Required - Electronic<br><input checked="" type="checkbox"/> Streamlined (Public only) |
| <b>Clinical criteria:</b>          | Patient must have undergone, be undergoing or be scheduled for an allogeneic haematopoietic stem cell transplant;<br>AND<br><del>The</del> Patient must have confirmed presence of cytomegalovirus-specific antibodies;<br>AND<br>The treatment must commence within 28 days of an allogeneic haematopoietic stem cell transplant.   |
| <b>Population criteria:</b>        | Patients must be 18 years of age or older.   |
| <b>Prescriber Instructions</b>     | For patients who are not concurrently taking cyclosporin and letermovir, two packs of 28 tablets will need to be requested and authorised for dispensing.  |
| <b>Administrative Advice</b>       | No increase in the maximum number of repeats will be authorised  |

- 2.2 The resubmission indicated that the requested restriction has been updated from that proposed in the initial submission to reflect the suggestions and additions proposed by the PBAC Secretariat and the PBAC in the July 2018 consideration of letermovir. The changes made were as follows: inclusion of clinical criteria to indicate when letermovir should be commenced; inclusion of criteria to restrict letermovir to those 18 years of age or older; inclusion of prescriber instructions for clarity of dosage for patients who do not concurrently receive cyclosporin and letermovir; removed criteria for when to measure antibodies and removed criteria for starting or not using letermovir in the presence of CMV infection; and alteration of the PBS indication for clarity. The PBAC considered that an age criterion was not required in the listing.
- 2.3 The requested restriction was largely consistent with the changes recommended by the PBAC in the July 2018 consideration of letermovir (paragraph 7.3 July 2018 Public Summary Document (PSD)). The ESC noted that the PBAC had advised that as patients undergoing a HSCT are regularly monitored by experienced clinical teams it was not necessary to include criteria related to not using letermovir in the presence of CMV infection (paragraph 7.3 July 2018 PSD). The ESC noted that in the pivotal trial (Trial P001) patients who developed CMV viraemia discontinued letermovir and commenced pre-emptive treatment (PET). Given the absence of evidence for the use of letermovir with PET the ESC expressed concern that neither the restriction nor the TGA approved Product Information (PI) specify the need to cease letermovir when PET is commenced. The ESC considered that inconsistencies in the use of terminology such as ‘prophylaxis’ across the resubmission and restriction raises concern over how this will be interpreted for letermovir in clinical practice.
- 2.4 The ESC also noted that Trial P001 excluded patients who had received a previous allogeneic HSCT. The ESC noted that the restriction did not exclude such patients and considered that this was appropriate given the proportion of patients receiving more than one HSCT was likely to be very low.

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

### **3 Background**

#### ***Registration status***

- 3.1 Letemovir was registered on the ARTG on 22 June 2018. The approved indication is: 'PREVYMIS is indicated for the prophylaxis of cytomegalovirus (CMV) infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT)'. The approved indication corresponded to the requested PBS restriction.
- 3.2 Letemovir was designated as an orphan drug by the TGA. The resubmission stated that letemovir had been granted regulatory approval in Canada (1 November 2017), the US (8 November 2017), the EU (8 January 2018), Japan (23 March 2018) and Switzerland (4 April 2018).

#### ***Previous PBAC consideration***

- 3.3 Following is a summary of the key concerns identified in the July 2018 PBAC submission and the response taken by the resubmission.

**Table 2: Summary of outstanding matters of concern**

| Component           | Matter of concern (July 2018)   | How the resubmission addresses it  |
|---------------------|---|--|
| Comparator          | Paragraph 7.4: PBAC considered that both placebo and antiviral treatments would be informative comparators.   | The resubmission nominated standard of care, i.e. the use of antiviral treatments as PET as per the current standard of practice, as the comparator (see 'Comparator' below for discussion).   |
| Clinical evidence   | Paragraph 7.5: 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 sequelae.  | The resubmission re-presented evidence provided in the July submission (although results for GVHD were excluded) and also included discussion of CMV-related mortality. The resubmission provided post-hoc analyses of CMV-related mortality and all-cause mortality to support its claim that letermovir is an effect modifier for the effect of CMV infection on mortality. The evidence presented did not support the resubmission's claim (see 'Comparative effectiveness' below for further discussion).                  |
| Economic evaluation | Paragraph 7.1: 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.<br>Paragraph 7.8: 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 different in the trial. 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. | The resubmission modified the economic evaluation – the GVHD health states were removed, survival was extrapolated using external data sources and CMV-related mortality from Trial P001 was applied for patients with CMV infection. Death events were limited to those observed in the trial period (24 and 48 weeks) and survival was extrapolated using ABMTRR data and ABS lifetables. The economic model did not directly consider a reduction in the use of PET (see 'Economic analysis' below for further discussion). |
| Financial estimates | Paragraph 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 resubmission has assumed the same treatment duration with letermovir (78 days) and has modified the proportion of patients using cyclosporin from █% used in July 2018 to █%. Overall, the resubmission has not provided a broad consideration of cyclosporin usage in the Australian population nor has the resubmission provided detailed consideration of the data presented, i.e. ABMTRR data from 2014 to 2016 (see 'Estimated PBS usage & financial implications' below for further discussion).                     |

ABMTRR=Australasian Bone Marrow Transplant Recipient Registry; CMV=cytomegalovirus; GVHD=graft versus host disease; PET=pre-emptive therapy; PSD=public summary document  
Source: July 2018 PSD; Table 1-1, p3-5 of the resubmission.

*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 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 seropositive. A sero-survey of CMV in Australia demonstrated that the population-weighted rate of CMV seropositivity in individuals aged between 1 to 59 years was 57%.

- 4.2 Following 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 The ESC noted that CMV infection is currently managed with prophylactic treatment or PET. PET involves initiation of antiviral therapy upon detection of active CMV infection through weekly blood testing. PET aims to treat the detected CMV infection and prevent development of symptoms and CMV disease. Prophylaxis involves initiation of antiviral therapy to all at-risk patients before active CMV infection is detected. The ESC noted that the meaning of prophylaxis in this context (i.e. initiation of antiviral therapy) is different to that intended in the letermovir restriction.
- 4.4 As in the July 2018 submission, letermovir is proposed for use as prophylactic therapy for CMV infection, with treatment commencing within 28 days of HSCT. The ESC considered that there was a clinical need for such therapy as there are no licensed treatments available on the PBS specifically for preventing CMV reactivation after an allogeneic HSCT.

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

## 5 Comparator

- 5.1 The resubmission nominated standard of care, i.e. the use of antiviral treatments as PET as per the current standard of practice, as the comparator. However, discussion of results in the resubmission referred to placebo as the comparator and listing was being sought for prophylaxis, not treatment of CMV infection.
- 5.2 The July 2018 submission used placebo as the comparator. The PBAC noted that the evidence, such as the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR) report, showed that antiviral treatments are used in Australian practice, either prophylactically or as PET, and their use would likely be reduced with the availability of letermovir. The PBAC considered that both placebo and antiviral treatments would be informative comparators (paragraph 7.4 July 2018 PSD).
- 5.3 The resubmission stated (p18) that the sponsor does not agree that a direct comparison to other antiviral treatments as prophylaxis would be informative, for the following reasons: other agents are not routinely used in Australia for prophylaxis; patients are usually managed with PET and in the vast majority of cases, letermovir would not replace any prophylaxis therapy but rather would be added on top of standard medical management, which is PET for the treatment of detected viraemia. The ESC noted that the ABMTRR report indicated approximately █% of 804 CMV seropositive patients and █% of 434 CMV seronegative patients received CMV prophylaxis over the 2014 to 2016 data collection period. The ESC noted that the ABMTRR report submitted with the July 2018 submission reported on whether ganciclovir use in this context in █ CMV seropositive patients was a pre-emptive strategy or primary prophylaxis. The ESC noted that PET accounted for █% of ganciclovir use in this context, █% was not PET (i.e. it was considered primary

prophylaxis) and in ■% of patients it was unknown whether use was classified as PET. The ESC considered that the ABMTRR report indicated that antivirals continue to be used as primary prophylaxis in Australia and that the distinction between prophylaxis and PET in Australian clinical practice is not clear cut. Hence, the ESC reaffirmed the July 2018 PBAC consideration that both placebo and antiviral treatments would be informative comparators. The pre-PBAC response argued that the current use of prophylaxis is difficult to determine using the ABMTRR because the registry includes an unclear breakdown of a wide range of antivirals (e.g. aciclovir, valaciclovir, famciclovir) which are used for a variety of viral infections such as varicella-zoster virus and human herpesvirus.

- 5.4 The resubmission also claimed that the clinical trial design inherently provides a comparison between letermovir prophylaxis and placebo prophylaxis on top of standard of care PET with other antivirals. Patients who received letermovir and developed CMV viraemia received PET to treat an active CMV infection as per the current standard of practice and therefore the trial evidence provides a comparison that is more aligned to clinical practice. However, the ESC noted that in the pivotal trial patients who developed CMV viraemia were required to discontinue letermovir, which would remove the possibility of a comparison. The PBAC agreed with the ESC and considered that the use of ganciclovir or other antivirals used before clinical viraemia was present would be an informative comparator in this context.
- 5.5 The resubmission also noted that an indirect comparison to ganciclovir prophylaxis would be based on studies published in 1993 for which there would be significant heterogeneity of the study design and lack of a consistent common comparator. Therefore, any conclusions from such a comparison (e.g. Gagelmann 2018) would not be informative for the current resubmission. The Gagelmann review had noted that it should be recognised that most ganciclovir studies were performed in the absence of PET which may introduce limitations to the generalisability of indirect comparisons of ganciclovir and new agents. The ESC noted that the Gagelmann 2018 review acknowledged the limitations of its meta-analysis and network meta-analysis but still drew the conclusion that the overall analysis suggested there was probably little or no difference in the effect of letermovir in preventing CMV disease compared with other antivirals, as noted by the PBAC in July 2018 (paragraph 7.6 July 2018 PSD).

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from health care professionals (3) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described the burden of CMV and highlighted that it remains a serious

cause of morbidity and mortality for people undergoing allogeneic HSCT. In addition the comments expressed concern regarding the toxicity of existing treatment options.

- 6.3 The PBAC noted the advice received from the Bone Marrow Transplant Society of Australia and New Zealand clarifying the likely use of letermovir in clinical practice. The PBAC noted the advice that current treatment revolves around PET with ganciclovir/valganciclovir and/or foscarnet, each of which has common toxicities which can limit treatment duration.

### Clinical trials

- 6.4 The resubmission was based on Trial P001, a randomised, double-blind Phase III trial comparing letermovir and placebo in CMV seropositive patients who had received an allogeneic HSCT. The July 2018 submission was based on the same trial. There are a limited number of letermovir trials available, those being the pivotal clinical trial (P001), a Phase II trial (Chemaly 2014), a trial in kidney transplant patients, and recently available on clinicaltrials.gov, a single arm open-label trial assessing use of letermovir for treatment of CMV infection and disease<sup>1</sup>. The proposed study P040 which is intended to compare efficacy outcomes in patients treated with 100 days versus 200 days of letermovir is not yet listed on clinicaltrials.gov.

- 6.5 Citation details of Trial P001 are provided in the table below.

**Table 3: Trials 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<br>Marty FM, Ljungman P, Chemaly RF, Maertens J, et al. Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation. | May 2017<br><br>NEJM 2017; 377(25):2433-2444 |

Source: Table 2-2, p31-32 of the resubmission.

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

**Table 4: Key features of the included evidence**

| Trial      | N                | Design/ duration   | Risk of bias | Patient population  | Outcomes   | Use in modelled evaluation           |
|------------|------------------|--|--------------|---|--|--------------------------------------|
| Trial P001 | 565 <sup>a</sup> | R, DB, MC<br>14 weeks treatment and follow-up through 48 weeks | Low          | CMV seropositive patients who were recipients of an allogeneic HSCT | CMV infection, CMV disease, mortality, re-hospitalisation, QoL | CMV infection, CMV-related mortality |

<sup>a</sup> 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; HSCT=haematopoietic stem cell transplant; MC=multi-centre; QoL=quality of life; R=randomised  
Source: Sections 2.2.3 to 2.4, p30-43 of the resubmission.

<sup>1</sup> For letermovir trials on clinicaltrials.gov see:

<https://clinicaltrials.gov/ct2/results?cond=&term=letermovir&cntry=&state=&city=&dist=>

- 6.7 The primary outcome in Trial P001 was the proportion of patients with clinically significant CMV infection at Week 24, a composite endpoint comprised of onset of CMV end-organ disease or initiation of PET based on documented CMV viraemia and the clinical condition of the patient.
- 6.8 The July 2018 submission included presentation of results for occurrence of graft versus host disease (GVHD) and this outcome was included in the July 2018 economic evaluation. The resubmission did not present results for GVHD and has removed this outcome from the economic model. The ESC noted that the resubmission provided post-hoc analyses of CMV-related mortality (all-cause mortality in patients who met the primary endpoint of clinically significant CMV infection) and included this outcome in the economic evaluation.
- 6.9 While there were 565 patients randomised to treatment in Trial P001, only 495 patients were analysed as patients with detectable CMV DNA on Day 1 of treatment were excluded from analysis. This was reasonable as these are the patients that are relevant to the requested listing.
- 6.10 When used with cyclosporin, letermovir is dosed at 240mg/day while when used alone, it is dosed at 480mg/day.
- 6.11 In Trial P001 51.9% of patients received concomitant treatment with cyclosporin. In the economic model and financial impact estimates the resubmission altered the proportion of patients assumed to use cyclosporin from the ■■■% applied in the July 2018 submission to ■■■% (see 'Estimated PBS usage & financial implications' below for discussion of the change in proportion using cyclosporin).

### ***Comparative effectiveness***

- 6.12 The resubmission provided the results for the primary outcome of Trial P001, the proportion of patients with the composite endpoint of clinically significant CMV infection through Week 24 post-transplant, based on both the non-completers=failure approach (failure defined as CMV infection, discontinuation or missing an outcome) and the data-as-observed approach (patients with missing values were excluded). The analysis using the data-as-observed approach was not presented in the July 2018 submission. The table below provides the results for both approaches to missing data. The ESC considered that the data-as-observed approach results were informative but advised that decision making should be based on review of the complete dataset.

**Table 5: Results for the primary outcome in Trial P001 – proportion of patients with clinically significant CMV infection**

|   | <b>Letermovir (N=325)</b><br>n % | <b>Placebo (N=170)</b><br>n % |
|---|----------------------------------|-------------------------------|
| <b>Non-completers=failure approach<sup>a</sup></b>    |                                  |                               |
| 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 <sup>a</sup>                           | 122 (37.5%)                      | 103 (60.6%)                   |
| <b>Stratum-adjusted treatment difference (95% CI)</b> | <b>-23.5 (-32.5, -14.6)</b>      |                               |
| <b>Data-as-observed approach<sup>b</sup></b>          |                                  |                               |
|   | <b>Letermovir (N=260)</b><br>n % | <b>Placebo (N=138)</b><br>n % |
| Clinically significant CMV infection by Week 24       | 57 (21.9%)                       | 71 (51.4%)                    |
| Initiation of PET                                     | 52 (20.0%)                       | 68 (49.3%)                    |
| CMV end-organ disease                                 | 5 (1.9%)                         | 3 (2.2%)                      |
| <b>Stratum-adjusted treatment difference (95% CI)</b> | <b>-30.7 (-40.3, -21.0)</b>      |                               |

<sup>a</sup> As the analysis assumed non-completers=failure, this total includes patients with CMV infection as well as those who discontinued or were missing outcome data at Week 24.

<sup>b</sup> Any patient with a missing value was excluded from the analysis.

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

Source: Table 2-9, p45 and Table 2-10, p46 of the resubmission.

6.13 With the analyses adjusted for low- and high-risk patients (risk of CMV reactivation) both approaches demonstrated a statistically significant lower risk of CMV infection for patients treated with letermovir.

6.14 The non-completers=failure approach was used as the primary approach for missing data. Based on this approach, the proportion with CMV infection was 17.5% in the letermovir group and 41.8% in the placebo group. Clinically significant CMV infection was a composite outcome including (i) onset of CMV end-organ disease and (ii) initiation of PET. The PBAC previously noted that the decrease in CMV infection associated with letermovir was due to a difference in the proportion of patients requiring PET (40.0% for letermovir versus 16.0% for placebo) but not the proportion with end-organ disease (1.8% versus 1.5%). As such, the difference between letermovir and placebo for proportion with clinically significant CMV infection was due to the difference in use of PET for CMV viraemia.

6.15 The resubmission provided a comparison of the initiation of PET, using the non-completer=failure approach, which demonstrated that a statistically significantly smaller proportion of letermovir-treated patients initiated PET. Results of this analysis are provided in the table below.

**Table 6: Proportion of patients initiating PET at Week 24 post-transplant**

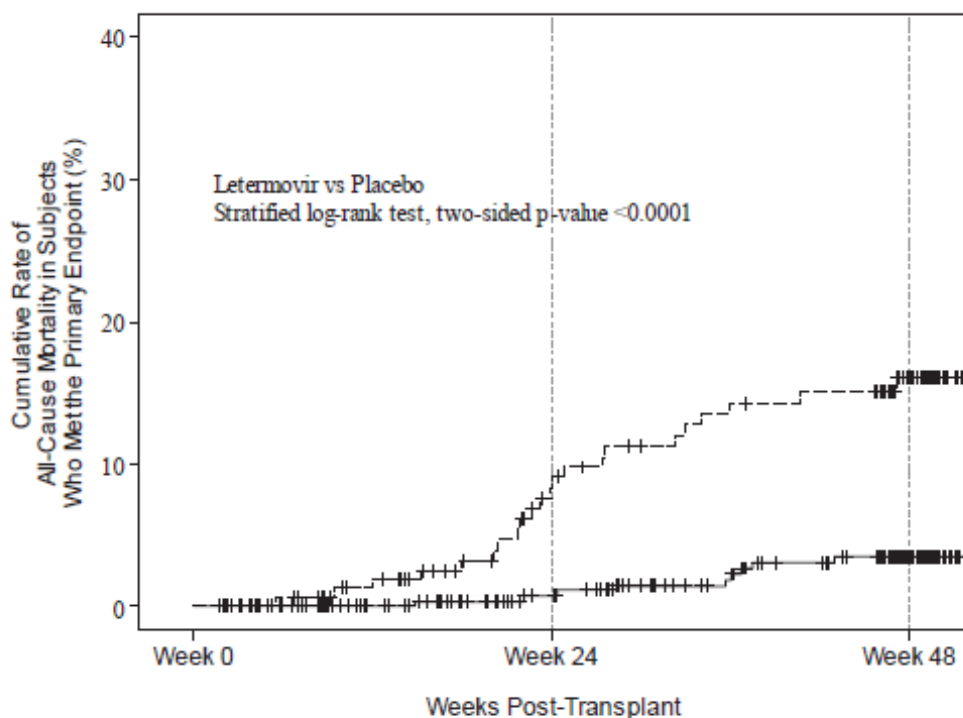
|   | <b>Letermovir (N=325)</b><br>n % | <b>Placebo (N=170)</b><br>n % |
|---|----------------------------------|-------------------------------|
| Initiation of PET                                     | 52 (16.0%)                       | 68 (40.0%)                    |
| Discontinued before Week 24                           | 57 (17.5%)                       | 28 (16.5%)                    |
| Missing outcome in Week 24 visit window               | 10 (3.1%)                        | 5 (2.9%)                      |
| Total failures  | 119 (36.6%)                      | 101 (59.4%)                   |
| <b>Stratum-adjusted treatment difference (95% CI)</b> | <b>-23.3 (-32.3, -14.3)</b>      |                               |

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

Source: Table 2-11, p46-47 of the resubmission.

- 6.16 The resubmission stated that the reduction in the proportion of patients initiating PET translated to improvements in mortality, re-hospitalisations and health-related quality of life (QoL). As noted below, the re-submission did not provide any evidence linking initiation of PET to re-hospitalisations and QoL, and the post-hoc analyses of mortality data did not support a link between initiation of PET and mortality.
- 6.17 The resubmission presented all-cause mortality data, as had been provided in the July 2018 submission, which showed a statistically significant advantage for letermovir at Week 24 ( $P=0.0327$ ) but no advantage at Week 48 ( $p=0.1224$ ).
- 6.18 The resubmission also presented the outcome of CMV-related mortality which was defined as all-cause mortality in patients who met the primary outcome of the trial (i.e. clinically significant CMV infection). The Kaplan-Meier mortality rate for letermovir-treated patients at 24 weeks was 0.7% compared to 9.1% for placebo-treated patients which was a statistically significant difference. At Week 48 the Kaplan-Meier mortality rate for letermovir-treated patients was 3.6% compared to 16.0% for placebo-treated patients which was also a statistically significant difference. The Kaplan-Meier plot for CMV-related mortality is provided below.

Figure 1: Kaplan-Meier plot of time to CMV-related mortality through Week 48 post-transplant in Trial P001



|               | No. at risk | KM estimates % (95% CI)                        |
|---------------|-------------|--|
| — Letermovir  | 325         | 262: 0.7 (0.0, 1.7)      138: 3.6 (1.3, 5.9)   |
| - - - Placebo | 170         | 125: 9.1 (4.3, 13.8)      71: 16.0 (9.9, 22.2) |

Source: Figure 2-3, p48 of the resubmission.

- 6.19 The PBAC previously noted (paragraph 6.20 July 2018 PSD) there was 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 July 2018 submission and the resubmission argued that the lack of statistical significance for all-cause mortality at Week 48 post-transplant may be due to the trial not being statistically powered to detect a difference at 48 weeks and the greater drop-out rate than anticipated. The drop-out rate between Week 24 and Week 48 was greater in the letermovir group (13.0%) than that observed in the placebo group (8.2%).
- 6.20 As CMV-related mortality referred to all-cause mortality in patients who met the primary outcome (i.e. clinically significant CMV infection), CMV infection may or may

not be related to mortality. This point was raised by the FDA<sup>2</sup> and CADTH<sup>3</sup> in their considerations of letermovir. To illustrate, a patient may have died due to a heart attack and if that patient had a CMV infection it would have been recorded as CMV-related mortality. There may be no difference in mortality related to CMV across the letermovir and placebo arms as the difference across the arms may have reflected differences in the incidence of clinically significant CMV infection. Therefore, the statistically significant advantage for letermovir for CMV-related mortality is difficult to interpret and may not reflect a difference in mortality attributable to CMV infection. The Pre-Sub-Committee Response (PSCR) argued that CMV-related mortality would only be recorded as directly related to CMV if the cause of death was a pathological process such as CMV pneumonitis or CMV colitis. The PSCR provided a list of the most common causes of all-cause mortality along with clinical opinion highlighting that ‘the attribution of cause of death in allogeneic bone marrow transplantation is extremely difficult’ to support its argument.

- 6.21 The resubmission provided post-hoc analyses of mortality outcomes, which it described as “Further analyses of the mortality outcomes from the clinical trial were undertaken to better understand the interaction of CMV infection and mortality post-transplant”. The resubmission provided within-group comparisons of all-cause mortality in patients with clinically significant CMV infection and those who did not have clinically significant CMV infection at Week 24 and Week 48. The results of these analyses are provided in the table below.

**Table 7: All-cause mortality in patients with and without clinically significant CMV infection – post-hoc analysis**

|                | Letermovir              |                             |                             | Placebo                 |                            |                             |
|----------------|-------------------------|-----------------------------|-----------------------------|-------------------------|----------------------------|-----------------------------|
|                | CMV infection<br>(N=57) | No CMV infection<br>(N=268) | HR <sup>a</sup><br>(95% CI) | CMV infection<br>(N=71) | No CMV infection<br>(N=99) | HR <sup>a</sup><br>(95% CI) |
| <b>Week 24</b> |                         |                             |                             |                         |                            |                             |
| Death n (%)    | █ (█%)                  | █ (█%)                      | (█, █)                      | █ (█%)                  | █ (█%)                     | (█, █)                      |
| <b>Week 48</b> |                         |                             |                             |                         |                            |                             |
| Death n (%)    | 9 (15.8%)               | 52 (19.4%)                  | 1.149<br>(0.556, 2.372)     | 22 (31.0%)              | 18 (18.2%)                 | 2.340<br>(1.174, 4.666)     |

<sup>a</sup> Results are provided as in the resubmission, with three decimal places.

CMV=cytomegalovirus; HR=hazard ratio

Source: Table 2-12, p49 of the resubmission.

- 6.22 The resubmission stated the analysis indicated that the occurrence of CMV infection increased the hazard of mortality through Week 48 by more than two times in those who received no prophylaxis (i.e. placebo group). The resubmission also stated that CMV infection was not associated with an increased hazard of mortality in the letermovir-treated group through Week 48 with a HR=1.149. The resubmission concluded that these results indicate letermovir is an effect modifier for the effect of

<sup>2</sup> FDA report available at:

[https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2017/209939Orig1s000,209940Orig1s000StatR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209939Orig1s000,209940Orig1s000StatR.pdf)

<sup>3</sup> CADTH clinical report available at:

[https://cadth.ca/sites/default/files/cdr/clinical/SR0545\\_Prevymis\\_CL\\_Report.pdf](https://cadth.ca/sites/default/files/cdr/clinical/SR0545_Prevymis_CL_Report.pdf)

CMV infection on mortality. The ESC considered that this conclusion was not strongly supported because:

- As outlined in paragraph 6.20, in Trial P001 CMV-related mortality referred to all-cause mortality in patients who met the primary outcome (i.e. clinically significant CMV infection). Therefore, mortality may not be related to CMV infection.
- The PSCR stated that if letermovir treatment was not an effect modifier for the effect of CMV infection on mortality, it would be expected that deaths unrelated to CMV infection would occur in equal proportions in the treatment and placebo arms given randomisation. The ESC noted that the mortality improvement claim was based on a naïve comparison of letermovir versus placebo via the two CMV infection versus no CMV infection within-group analyses summarised in Table 7. The ESC considered that, as randomisation has been broken, it can no longer be assumed that imbalances in confounders in the infection sub-groups are being controlled which limits any comparison of the hazard ratios presented.
- In addition, little information on the methodology used for the post-hoc analyses was provided by the resubmission. While it was stated that the comparisons were adjusted for age, there was no discussion around why the comparisons were adjusted for age or how these results may have differed from those not adjusted for age. The resubmission only provided visual comparisons of hazard ratios for each within-group comparison and did not provide between-group statistical comparisons of the CMV infection and no CMV infection subgroups for letermovir and placebo-treated patients. The PSCR provided a proportional hazard model for all-cause mortality through week 48 post-HSCT (p5 Table 2 and Appendix 2) to investigate the differential effect of CMV infection on mortality by treatment group. The PSCR stated that a Cox regression model was fitted to estimate the treatment effect in patients with and without CMV infection by adding CMV infection (as a time-dependent variable) and interaction between CMV infection and treatment into the selected model, whilst controlling for age, acute GVHD grades II-IV, baseline CMV risk for reactivation (high vs low) and age (10 year groups). The ESC noted that the hazard ratio for all-cause mortality was 0.45 (95% CI, 0.21-1.00; P=0.05) for letermovir versus placebo among patients who developed clinically significant CMV infection through Week 24; and the HR was 1.05 (95% CI, 0.61-1.81; p = 0.85) for letermovir versus placebo among patients who did not develop clinically significant CMV infection. The ESC was concerned that the comparisons were not adjusted for other predictors of all-cause mortality (e.g. disease course or previous treatments). The ESC considered that the ongoing confounder imbalance for those predictors not included in the multivariate Cox regression model presented in the PSCR coupled with the borderline insignificant hazard ratio for letermovir versus placebo among patients who developed clinically significant CMV infection made it difficult to claim any clear mortality benefit favouring letermovir from the data presented. The pre-PBAC response acknowledged the borderline insignificant hazard ratio but also highlighted the challenges associated with undertaking a study that is adequately powered to

detect a mortality benefit in allogeneic HSCT patients, especially when utilising the surrogate endpoint of CMV infection which is known to increase the risk of mortality. The PBAC disagreed with the sponsor and considered that based on the size of the modelled mortality benefit that Trial P001 would have been adequately powered to detect such a difference.

- 6.23 The resubmission also cited an advantage in re-hospitalisations for patients with clinically significant CMV infection. These data are provided below, statistical comparisons were not presented.

**Table 8: Patients with re-hospitalisation after clinically significant CMV infection**

| <b>Clinically significant CMV infection + discontinued + missing data</b> | <b>Letermovir (N=122)</b> | <b>Placebo (N=103)</b> |
|---|---------------------------|------------------------|
| Re-hospitalisation for CMV infection/disease                              | 10 (8.2%)                 | 13 (12.6%)             |
| <b>Clinically significant CMV infection</b>                               | <b>Letermovir (N=57)</b>  | <b>Placebo (N=71)</b>  |
| Re-hospitalisation for CMV infection/disease                              | 10 (17.5%)                | 13 (18.3%)             |

Source: Table 2-14, p53 and Table 2-9, p45 of the resubmission and proportions calculated during the evaluation.

- 6.24 The ESC noted that while the proportion with re-hospitalisation was lower for letermovir-treated patients (8.2%) compared to placebo-treated patients (12.6%) when the denominator included discontinued patients and those with missing data, the proportions were similar between letermovir and placebo (17.5% and 18.3%) when only those who were identified as having CMV infection are included in the denominator. As such, the ESC considered there is little support for the resubmission’s claim that the differences between groups in re-hospitalisation may have been due to the lower incidence of clinically significant CMV infection in the letermovir group.

- 6.25 The resubmission did not provide any results for the occurrence of bacterial and fungal infections but noted that CMV infection is associated with an increased risk of bacterial and fungal infections. The trial Clinical Study Reports (CSR) provided results for this outcome, which are summarised in the table below at Week 24 and Week 48.

**Table 9: Patients with bacterial or fungal infections**

|                                   | <b>Letermovir (N=325)</b> | <b>Placebo (N=170)</b> |
|-----------------------------------|---------------------------|------------------------|
| <b>Week 24</b>                    |                           |                        |
| Bacterial and/or fungal infection | 87 (26.8%)                | 43 (25.3%)             |
| <b>Week 48</b>                    |                           |                        |
| Bacterial and/or fungal infection | 112 (34.5%)               | 55 (32.4%)             |

Source: Table 11-21, p222 of P001V01 CSR and Table 11-6, p95 of P001V02 CSR.

- 6.26 The ESC noted that the occurrence of bacterial and/or fungal infections was numerically slightly higher for letermovir-treated patients at both Weeks 24 and 48 which did not concur with the lower incidence of clinically significant CMV infection observed in letermovir-treated patients.
- 6.27 As for the July 2018 submission, the resubmission provided a summary of change from baseline in EQ-5D index scores, EQ-5D VAS scores and FACT-BMT scores. The post-hoc comparisons of change from baseline QoL scores had been presented in the PSCR for the July 2018 submission. The table below provides the results of the analyses for the change from baseline QoL scores for the EQ-5D for the week 14, Week 24 and Week

48 time points, which were used in the economic model. Results for CMV infection/discontinuation visits, which were included in the economic model, were also provided, but no statistical comparisons were provided for these data.

**Table 10: Results for the analysis of change from baseline QoL scores in Trial P001**

|                                | Baseline          |                   | Week 14 post-transplant |                   | Week 24 post-transplant |                   | Week 48 post-transplant |                   | All infection/discontinuation visits <sup>a</sup> |     |
|--------------------------------|-------------------|-------------------|-------------------------|-------------------|-------------------------|-------------------|-------------------------|-------------------|---|-----|
|                                | Leter             | PBO               | Leter                   | PBO               | Leter                   | PBO               | Leter                   | PBO               | Leter   | PBO |
| <b>EQ-5D Index scores</b>      |                   |                   |                         |                   |                         |                   |                         |                   |   |     |
| N                              | 243               | 135               | 193                     | 98                | 149                     | 72                | 142                     | 74                |   |     |
| Mean (SD)                      | 0.639<br>(0.3438) | 0.669<br>(0.2854) | 0.753<br>(0.2867)       | 0.720<br>(0.2836) | 0.751<br>(0.2859)       | 0.758<br>(0.2701) | 0.786<br>(0.2503)       | 0.768<br>(0.2856) |   |     |
| Mean change from baseline (SE) | -                 | -                 | 0.107<br>(0.3726)       | 0.025<br>(0.3540) | 0.108<br>(0.3822)       | 0.040<br>(0.3738) | 0.164<br>(0.3534)       | 0.084<br>(0.3840) |   |     |
| Mean difference (95% CI)       | -                 |                   |                         |                   |                         |                   |                         |                   | NR  |     |

<sup>a</sup> Mean change from baseline scores for all infection/discontinuation visits are mean (SD).

EQ-5D=EuroQoL 5 Dimensions; FACT-BMT=Functional Assessment of Cancer Therapy – Bone Marrow Transplant; Leter=letermovir; NR=not reported; PBO=placebo; SD=standard deviation; SE=standard error

Source: Table 2-16, p56 of the resubmission.

6.28 The ESC noted that there were no observed differences between the letermovir and placebo groups in change from baseline in QoL measures.

### Comparative harms

6.29 In regard to the July 2018 submission the PBAC had considered that a claim of non-inferior safety compared to placebo was appropriate, agreeing with ESC that it was reasonable to conclude that AEs reported in the submission were comparable between the arms of the trial (paragraph 7.7 July 2018 PSD). The clinical claim with respect to safety remained the same as for the July 2018 submission.

6.30 The resubmission presented safety outcomes as had been presented in the July 2018 submission, along with statistical comparisons for the overall AEs, and a discussion of cardiac-related events. The latter two are summarised below.

**Table 11: Results of statistical comparisons of adverse event data**

| Adverse event             | Letermovir N=373<br>n (%) | Placebo N=192<br>n (%) | RR/OR<br>(95% CI)                    |
|---------------------------|---------------------------|------------------------|--------------------------------------|
| One or more AE            | 365 (97.9%)               | 192 (100%)             | <b>0.22 (0.05, 0.94)<sup>a</sup></b> |
| Serious AE                | 166 (44.5%)               | 92 (47.9%)             | 0.93 (0.77, 1.12)                    |
| Discontinuation due to AE | 73 (19.6%)                | 99 (51.6%)             | <b>0.38 (0.30, 0.49)</b>             |
| Drug-related AE           | 63 (16.9%)                | 25 (13.0%)             | 1.30 (0.84, 1.99)                    |
| Serious drug-related AE   | 3 (0.8%)                  | 3 (1.6%)               | 0.49 (0.09, 2.66) <sup>a</sup>       |

<sup>a</sup> Peto odds ratio was used instead of relative risk if incidence was ≤1% or ≥99% in at least one cell.

AE=adverse event; CI=confidence interval; OR=odds ratio; RR=relative risk; **bold**=statistically significant

Source: Table 2-18, p58 of the resubmission.

6.31 There were statistically significantly fewer letermovir-treated patients reporting one or more AEs and discontinued from the trial for AEs compared to placebo-treated patients, with no statistically significant differences between the groups for serious AEs, drug-related AEs or serious drug-related AEs.

6.32 The resubmission provided a tabled summary of cardiac-related AEs including absolute difference in percentage between letermovir and placebo-treated patients. These AEs are provided in the table below.

**Table 12: Cardiac-related AEs in Trial P001**

| Adverse event       | Letermovir N=373<br>n (%) | Placebo N=192<br>n (%) | Difference in %<br>(95% CI) |
|---------------------|---------------------------|------------------------|-----------------------------|
| Cardiac disorders   | 47 (12.6%)                | 12 (6.3)               | 6.4% (1.1%, 11.0%)          |
| Atrial fibrillation | 13 (3.5%)                 | 2 (1.0%)               | 2.4% (-0.5%, 5.0%)          |
| Atrial flutter      | 4 (1.1%)                  | 0 (0.0%)               | 1.1% (0.9%, 2.7%)           |
| Cardiac failure     | 5 (1.3%)                  | 0 (0.0%)               | 1.3% (-0.6%, 3.1%)          |
| Sinus tachycardia   | 4 (1.1%)                  | 3 (1.6%)               | -0.5% (3.5%, 1.5%)          |
| Tachycardia         | 15 (4.0%)                 | 4 (2.1%)               | 1.9% (1.5%, 4.8%)           |

AE=adverse event; CI=confidence interval

Source: unnumbered table, p61 of the resubmission.

6.33 As noted by the resubmission, the incidence of cardiac-related AEs was higher in the letermovir group compared to the placebo group. The pre-PBAC response for the July 2018 submission noted that the TGA Delegate’s Overview had concluded that the majority of events were non-serious, of mild to moderate severity and confounded by concomitant use of known cardiotoxic medications, cardiac history, acute infections and possible imbalance in baseline cardiac conditions between the letermovir and placebo arms.

6.34 The resubmission stated that a post-hoc analysis was conducted to evaluate the imbalance in cardiac-related AEs across the treatment groups, and that this analysis examined potential confounding factors such as medical history, concurrent conditions and treatments, the association with study medication (temporal and route of administration) and information on de-challenge or re-challenge.

6.35 The background information included in the resubmission on pre-existing or active medical conditions provided relevant information for observed cardiac-related AEs categorised as serious and/or when a patient discontinued treatment. However, the background information did not address reasons for the greater incidence of cardiac-related AEs in letermovir treated patients across all occurrences of these events.

### **Benefits/harms**

6.36 On the basis of the direct evidence presented by the resubmission (see Table 5 above), 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).

### **Clinical claim**

- 6.37 The resubmission described letermovir as superior in terms of effectiveness compared with placebo and non-inferior in terms of safety compared to placebo. This was the same as the clinical claim made by the July 2018 submission.
- 6.38 The clinical evidence demonstrated a statistically significant reduction in CMV infection for letermovir-treated patients. The ESC reaffirmed the PBAC's July 2018 observation that the reduction was due to the difference in the use of PET for CMV viraemia (paragraph 7.5 July 2018 PSD).
- 6.39 The ESC noted that the clinical evidence for CMV-related mortality indicated a statistically significant difference between letermovir and placebo at week 48. However, as CMV-related mortality in Trial P001 referred to all-cause mortality in patients who met the primary outcome of clinically significant CMV infection, the ESC considered CMV infection may not be related to mortality. As such, the statistically significant advantage for letermovir for CMV-related mortality was difficult to interpret and may not reflect a difference in mortality attributable to letermovir treatment.
- 6.40 In addition, the ESC considered that the post-hoc analysis of all-cause mortality in patients with and without clinically significant CMV infection did not demonstrate that letermovir is an effect modifier for the effect of CMV infection on mortality, as claimed by the resubmission and PSCR .
- 6.41 The resubmission cited an advantage in re-hospitalisations for patients with CMV infection. The ESC noted that when discontinued and missing patients were excluded from the comparison, the proportion re-hospitalised was similar between the letermovir and placebo groups.
- 6.42 While the resubmission did not provide any results for the occurrence of bacterial and fungal infections, which is considered to be associated with CMV infection, the ESC noted that the results in the Trial P001 CSRs showed no difference in the occurrence of bacterial and/or fungal infections for letermovir-treated versus placebo-treated patients.
- 6.43 The ESC noted that the claim of non-inferior safety compared to placebo had been previously accepted by the PBAC (paragraph 7.7 July 2018 PSD). While the resubmission provided further discussion around the occurrence of cardiac-related events in Trial P001 the resubmission provided no information around planned further evaluation in future studies, as recommended by the PBAC (paragraph 7.7 July 2018 PSD).
- 6.44 The PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data. The PBAC considered the reduction in CMV infection for letermovir-treated patients appeared to be based on the difference in the use of PET for CMV viraemia only, with no clear differences attributable to letermovir in mortality, CMV disease, re-hospitalisations or occurrence of bacterial or fungal infections.

6.45 The PBAC considered that the claim of non-inferior comparative safety was reasonably supported by the data.

### **Economic analysis**

6.46 The economic model presented in the resubmission was revised from that presented in the July 2018 submission as outlined in the table below. This table also includes the PBAC and ESC comments on the July 2018 model.

**Table 13: July 2018 economic evaluation, PBAC and ESC comments and changes to the current model**

| July 2018 model   | PBAC/ESC comments (July 2018 PSD)  | Resubmission model  |
|---|--|---|
| Overall   | <u>Paragraph 7.8</u> : 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 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.  | The revised model removed GVHD health states but reduction in use of PET was not directly considered as part of the model (although cost of PET for treatment of CMV infection was included in the model).  |
| Markov model with a 10 year duration  | <u>Paragraph 6.46</u> : 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.   | In the revised model the 10 year time horizon has been maintained and extrapolation of mortality data has been modified.  |
| 7 health states: post-transplant; CMV infection; CMV disease; acute GVHD Grade II, acute GVHD Grade III-IV, chronic GVHD, death | <u>Paragraph 6.43</u> : 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.  | Revised model included 4 health states: post-transplant; CMV infection; post CMV infection; death.  |
| Mortality data was extrapolated from Week 1 to 10 years.  | <u>Paragraph 6.41</u> : 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). The ESC noted that the 10 year survival data in the ABMTRR annual report 2016 broadly supported the conclusions of Wingard 2011. | In the revised model for patients who develop CMV infection, CMV-related mortality data from Trial P001 at Week 24 and Week 48 was applied, followed by updated ABMTRR data and then natural mortality sourced from lifetables. For patients who do not develop CMV infection, ABMTRR data for 3 years was applied followed by natural mortality sourced from lifetables. |
| Utility values were literature-based  | <u>Paragraph 6.42</u> : The ESC 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 as to why trial-based values were not considered for use in the economic model.   | Trial-based utility values were applied in the revised model.   |
| Model assumed 78 days of letermovir treatment   | <u>Paragraph 6.45</u> : The ESC considered that in practice nearly all patients will be treated for a period longer than 78 days.  | Treatment duration of 78 days has been maintained in the revised model.   |

ABMTRR=Australasian Bone Marrow Transplant Recipient Registry; CMV=cytomegalovirus; GVHD=graft versus host disease; PSD=public summary document

Source: Section 3.1 of the resubmission.

- 6.47 The ESC noted that the key changes to the economic model were removal of the GVHD health states, alteration of extrapolation for mortality data (parametric distributions of trial-based data used in the July 2018 model were replaced by trial data to 2 years, ABMTRR data for 3 years and natural mortality sourced from lifetables for the remainder of the model duration) and use of Trial P001 data for utility values. The resubmission stated (p81) that no extrapolation was applied for mortality; however, survival was extrapolated using external data sources, i.e. ABMTRR data and ABS lifetables.
- 6.48 The ESC noted the model was designed to assess the impact of letermovir on CMV infections and associated mortality. However, the ESC considered the clinical data do not adequately support a mortality benefit with letermovir. The pre-PBAC response stated that the economic model presented in this resubmission aims to replicate the health benefits that would be observed in the healthcare system with the introduction of letermovir. The pre-PBAC response argued that therefore, the health benefits of letermovir treatment demonstrated in the clinical trial are not limited to the reduction in the use of PET, but also to reduced mortality risk. The PBAC agreed with the ESC that a mortality benefit could not clearly be attributed to letermovir based on the evidence provided in the resubmission.
- 6.49 A summary of the key drivers of the economic model is provided in the table below.

**Table 14: Key drivers of the model**

| Description   | Method/Value  | Impact                   |
|---|---|--------------------------|
| Probability of clinically significant CMV infection | While Trial P001 demonstrated a statistically significant advantage of letermovir compared to placebo for the occurrence of clinically significant CMV infection the application of these data in the revised model has been altered from that used in the July 2018 model and could not be tested in sensitivity analyses given lack of detail provided on the derivation of probabilities by the resubmission. As the occurrence of CMV is a key difference between letermovir and placebo these probabilities will impact model results. | High, favours letermovir |
| Assumed link between CMV infection and mortality    | The resubmission maintained that letermovir was an effect modifier for the effect of CMV infection on mortality and on this basis included mortality risks in the model linked to CMV-related mortality. The evidence presented by the resubmission did not support a link between letermovir treatment and mortality.  | High, favours letermovir |

Compiled from Section 2.5.1 and Section 3 of the resubmission during the evaluation.

- 6.50 The results of the economic evaluation are provided in the table below. Base case results of the July 2018 economic evaluation are provided for reference. The ESC considered that the resulting ICER was very uncertain due to concerns around the mortality and QoL inputs in the model.

**Table 15: Results of the stepped economic evaluation**

| Step and component   | Letemovir     | Placebo       | Increment     |
|--|---------------|---------------|---------------|
| <b>Step 1: Trial-based costs and outcomes</b>                    |               |               |               |
| Costs  | \$ [REDACTED] | \$0           | \$ [REDACTED] |
| Proportion with clinically significant CMV infection             | 37.5%         | 60.6%         | 23.1%         |
| Incremental cost/clinically significant CMV infection avoided    |               |               | \$ [REDACTED] |
| <b>Step 2: Trial-based costs and outcomes including PET</b>      |               |               |               |
| Costs  | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| Proportion with clinically significant CMV infection             | 37.5%         | 60.6%         | 23.1%         |
| Incremental cost/clinically significant CMV infection avoided    |               |               | \$ [REDACTED] |
| <b>Step 3: Model duration to 10 years and life years applied</b> |               |               |               |
| Costs  | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| LYG  | 4.86          | 4.56          | 0.30          |
| Incremental cost/extra LY gained                                 |               |               | \$ [REDACTED] |
| Incremental cost/extra LY gained (July 2018)                     |               |               | \$ [REDACTED] |
| <b>Step 4: Cost-utility analysis at 10 years</b>                 |               |               |               |
| Costs  | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| QALY   | 3.78          | 3.47          | 0.31          |
| Incremental cost/extra QALY gained (base case)                   |               |               | \$ [REDACTED] |
| Incremental cost/extra QALY gained (July 2018 base case)         |               |               | \$ [REDACTED] |

Source: Table 3-12, p91-92 of the resubmission.

6.51 There are a number of issues with the revised economic model:

- The probability of clinically significant CMV infection (the key clinical outcome in Trial P001) applied in the economic model could not be tested in a meaningful way. The ESC noted that while the same source data as used in the July 2018 model was used, the resubmission applied rates (37.5% for letemovir versus 60.6% for placebo) that were different to those applied in the July 2018 model (17.2% versus 42.4%) and included those that discontinued treatment and had missing outcome data. The PSCR stated the original approach was inappropriate to model the actual infection rate in clinical practice, as patients who developed a CMV infection and discontinued from the study before week 24 were not captured. The PSCR also stated that published evidence (Nakamae et al 2009 and Green et al 2016) supported rates of CMV infection in seropositive patients undergoing a HSCT that are similar to the revised rates used in the resubmission. The ESC questioned the appropriateness of applying this revised methodology in the model.
- While the resubmission indicated that the rates of 37.5% for letemovir and 60.6% were used to determine the probability of CMV infection applied in the model, the model results showed that at Week 24 12.4% of letemovir-treated patients had CMV infection (range of 1.9% to 17.2% across the 24 weeks), which was less than the 17.5% observed in Trial P001 at Week 24. For placebo-treated patients the model showed that 16.6% of patients had CMV infection at Week 24 (range of 3.8% to 30.2%), which was less than the 41.8% observed in the trial. The PSCR stated that the apparent discrepancy between trial-based clinically significant CMV infections and mortality figures in the model arises from the structural

difference between Markov models and trial endpoint reporting. The ESC disagreed, and remained concerned that the application of the probability of CMV infection in the model may not accurately reflect trial-based values.

- Sensitivity analyses could not be conducted to address the resubmission's assumption of the same duration of PET (59.3 days) in both arms, when Trial P001 indicated a longer duration for letermovir-treated patients (60.4 days compared to 58.5 for placebo). In general, the lack of variables able to be tested in sensitivity analyses limited the informativeness of the model.
- The resubmission's model applied mortality probabilities at Week 24 and Week 48 for patients with CMV infection, as the resubmission had claimed that the CMV-related mortality results indicated letermovir was an effect modifier for the effect of CMV infection on mortality. The ESC considered there was little support for the resubmission's claim around CMV infection and mortality (see 'Comparative effectiveness'). In addition, the ESC did not accept the resubmission and PSCR claim that letermovir is an effect modifier for the effect of CMV infection on mortality.
- The ESC considered that there was also little support for the re-submission's claim that the differences between groups in re-hospitalisation may have been due to the lower incidence of clinically significant CMV infection in the letermovir group.
- The ESC noted that the utility values applied in the revised model were lower than the values applied in the July 2018 model. However, the ESC considered they still appeared somewhat high for unwell patients. In addition, the ESC noted that the utility value for patients with CMV infection was similar to that for patients without CMV infection, particularly in the letermovir arm. The ESC considered that it may not be reasonable to assume a QoL gain with letermovir given there were no statistically significant differences reported for this outcome between letermovir and placebo-treated patients in Trial P001.
- The resubmission has maintained the assumption of 78 days of letermovir treatment and decreased the proportion of patients using cyclosporin to █%. The resubmission has not provided a comprehensive consideration of historical trends in the use of cyclosporin (see 'Estimated PBS usage & financial implications' below for further detail) and treatment duration is likely to be longer than 78 days (paragraph 6.45 July 2018 PSD). The ESC considered that it may be more appropriate to increase the duration of therapy to 100 days (the recommended duration) or 112 days (as available under the requested restriction) which increased the ICER to \$15,000/QALY to \$45,000/QALY and \$15,000/QALY to \$45,000/QALY respectively from a base case of \$15,000/QALY to \$45,000/QALY. The ESC also considered that concerns remained around the proportion of patients using cyclosporin and the impact that variation in use from that predicted would have on the ICER. Hence, the ESC considered the cost of letermovir in the economic model may not reflect the cost associated with potential use in clinical practice.

6.52 A summary of key sensitivity analyses are provided in the table below.

**Table 16: Sensitivity analyses of the economic evaluation**

| Analyses  | Incremental cost | Incremental QALY | ICER          |
|---|------------------|------------------|---------------|
| <b>Base case</b>  | \$ [REDACTED]    | 0.31             | \$ [REDACTED] |
| Time horizon (base case: 10 years)  |                  |                  |               |
| 5 years   | \$ [REDACTED]    | 0.20             | \$ [REDACTED] |
| 2 years   | \$ [REDACTED]    | 0.10             | \$ [REDACTED] |
| 1 year  | \$ [REDACTED]    | 0.04             | \$ [REDACTED] |
| Treatment duration (base case: 78 days)   |                  |                  |               |
| 100 days  | \$ [REDACTED]    | 0.31             | \$ [REDACTED] |
| 112 days  | \$ [REDACTED]    | 0.31             | \$ [REDACTED] |
| Utility value – (base case: Trial P001)   |                  |                  |               |
| Weighted average Trial P001 values  | \$ [REDACTED]    | 0.24             | \$ [REDACTED] |
| CMV utility 0.705 for letermovir and placebo  | \$ [REDACTED]    | 0.31             | \$ [REDACTED] |
| Hospitalisation cost (base case: \$13,848)  |                  |                  |               |
| \$6,942 (-50%)  | \$ [REDACTED]    | 0.31             | \$ [REDACTED] |
| \$20,772 (+50%)   | \$ [REDACTED]    | 0.31             | \$ [REDACTED] |
| Proportion hospitalised (base case 8.2% letermovir and 12.6% placebo)                                     |                  |                  |               |
| 5% both arms  | \$ [REDACTED]    | 0.31             | \$ [REDACTED] |
| 10% both arms   | \$ [REDACTED]    | 0.31             | \$ [REDACTED] |
| Mortality (base case: trial-based <sup>a</sup> Weeks 24 and 48; ABMTRR for 3 years; lifetables remainder) |                  |                  |               |
| Placebo arm using ABMTRR data   | \$ [REDACTED]    | 0.34             | \$ [REDACTED] |
| Trial-based probability increased by 50%  | \$ [REDACTED]    | 0.50             | \$ [REDACTED] |
| Trial-based probability decreased by 50%  | \$ [REDACTED]    | 0.08             | \$ [REDACTED] |
| Probability of CMV infection (base case: letermovir 0.0194; placebo 0.0381)                               |                  |                  |               |
| Trial-based probability increased by 50%  | \$ [REDACTED]    | 0.41             | \$ [REDACTED] |
| Trial-based probability decreased by 50%  | \$ [REDACTED]    | 0.20             | \$ [REDACTED] |
| Time horizon (base case: 10 years) and treatment duration (base case: 78 days)                            |                  |                  |               |
| 5 years and 100 days  | \$ [REDACTED]    | 0.20             | \$ [REDACTED] |

<sup>a</sup> The trial-based probability for mortality at Week 24 was 0.0023 for letermovir and 0.0091 for placebo. At Week 48 the values applied were 0.0036 for letermovir and 0.0077 for placebo.

CMV=cytomegalovirus; PET=pre-emptive therapy

Source: Table 3-16, p95-97 of the resubmission.

The redacted table shows ICERs in the range of less than 15,000/QALY to \$200,000/QALY

6.53 The ESC noted that the economic model demonstrated sensitivity to the model time horizon and letermovir treatment duration. Decreasing model duration to 5 years increased the ICER to \$15,000/QALY to \$45,000/QALY from the base case \$15,000/QALY to \$45,000/QALY. Increasing letermovir treatment duration to 100 days increased the ICER to \$15,000/QALY to \$45,000/QALY. Applying both changes concurrently increased the ICER to \$45,000/QALY to 75,000/QALY.

6.54 The ESC noted that the model also demonstrated sensitivity to hospitalisation costs, with the ICER varying when this cost was increased or decreased and also when the proportion hospitalised was altered. Utility values were trial based and the sensitivity analyses, which also were trial-based, showed little impact on the ICER.

6.55 The resubmission provided no sensitivity analyses of the probability of CMV infection, the key clinical outcome in Trial P001. If a 50% decrease in the probability of CMV infection was assumed the ICER increased to \$45,000/QALY to 75,000/QALY and if a 50% increase was assumed the ICER decreased to less than \$15,000/QALY.

6.56 For mortality the resubmission presented a sensitivity analysis using ABMTRR data in the placebo arm; this increased the ICER to \$15,000/QALY to \$45,000/QALY. Applying a 50% increase to the mortality rates decreased the ICER to less than \$15,000/QALY. Applying a 50% decrease to the mortality rate increased the ICER to \$75,000/QALY to \$105,000/QALY. This demonstrates the model result is sensitivity to the assumed probability of CMV-related mortality. The clinical evidence presented by the resubmission did not conclusively demonstrate a difference in mortality attributable to letermovir treatment and CMV infection.

**Drug cost/patient/course**

6.57 The resubmission provided the cost of letermovir assuming a treatment duration of 78 days. The cost provided was based on the assumption that █% of patients would use cyclosporin and also included a portion of patients discontinuing drug due to death. The July 2018 submission had not included drug discontinuation due to death in its estimate. The cost of treatment with letermovir as presented by the resubmission is provided in the table below, along with the July 2018 cost for reference. Costs for additional treatment durations (100 days as recommended in the PI and 112 days as available under the requested restriction) are also provided.

**Table 17: Letermovir treatment cost**

| Dose                                      | Cost/day (\$█/pack) | Treatment duration                            | Treatment cost   |
|---|---------------------|---|------------------|
| <b>Resubmission</b>                       |                     |   |                  |
| █% using 240mg/day and █% using 480mg/day | \$█                 | 78 days – Trial P001 and as used in the model | \$█ <sup>a</sup> |
|   |                     | 100 days as recommended in PI                 | \$█ <sup>a</sup> |
|   |                     | 112 days as under requested restriction       | \$█ <sup>a</sup> |
| <b>July 2018 submission</b>               |                     |   |                  |
| █% using 240mg/day and █% using 480mg/day | \$█                 | 78 days – Trial P001 and as used in the model | \$█              |
|   |                     | 100 days as recommended in PI                 | \$█              |
|   |                     | 112 days as under requested restriction       | \$█              |

<sup>a</sup> All treatment costs produced by the resubmission model included patients who had discontinued due to death.

Source: Section 3.8.2 of the resubmission and 5.07.COM.93.

6.58 The decrease in letermovir treatment cost compared to the July 2018 submission is largely due to the consideration of discontinued patients as presented by the resubmission, as the July 2018 treatment cost estimates did not include deaths as predicted by the model. Using the █% cyclosporin proportion and assuming no discontinuation due to death resulted in a treatment cost of \$█ for letermovir.

6.59 The accuracy of the letermovir treatment cost depends on the assumed treatment duration, the proportion of patients concomitantly treated with cyclosporin and proportion of patients discontinuing treatment. Treatment duration may have been underestimated by the resubmission.

**Estimated PBS usage & financial implications**

6.60 This resubmission was not considered by DUSC. As for the July 2018 submission the resubmission applied an epidemiological approach to estimate the number of patients treated with letermovir. The resubmission altered its determination of eligible patients (based on AIHW procedure codes for allogeneic bone marrow or stem cell

transplants in Australia) by expanding the number of years of AIHW procedure codes used (2011 to 2017) and also altering the assumed growth rate in transplant procedures (decreased to 3.68% from 4.58% used in July 2018). The use of this lower growth rate resulted in the estimated eligible patient numbers being less than that estimated in the July 2018 submission (while the July 2018 submission did not provide an estimate of eligible patient numbers for Year 6, was assumed that numbers were similar to those estimated for Year 5). The same proportion of adult patients (82%) and seropositive patients (65%) sourced from ABMTRR data were used, as was the same uptake rate of 90% across all years of listing.

- 6.61 In regard to determination of the proportion of patients using cyclosporin, the PBAC considered further evidence to show historical long-term trends in cyclosporin use in HSCT would assist in addressing the uncertainty of the assumption of cyclosporin usage in █% of Australian patients (paragraph 7.9 July 2018 PSD).
- 6.62 The resubmission stated (p97) that historical trends in cyclosporin use in HSCT were presented. However, the resubmission has not presented data outside of the years included in the ABMTRR report presented with the July 2018 submission, which included cyclosporin usage in patients between 2014 and 2016. The resubmission has presented the ABMTRR data by year (2014, 2015, 2016) while in the July 2018 submission all years were grouped together. The resubmission has also changed the source of the estimate of cyclosporin use to be based on all transplant recipients (seropositive and seronegative) in 2016 only (█%). This differed from the July 2018 submission where seropositive patients across 2014 to 2016 provided the estimate of cyclosporin use (█%). The resubmission has identified the revised estimate of cyclosporin use as the 'most up to date'. There does not appear to have been a consideration of cyclosporin use prior to 2014 or following 2016.
- 6.63 In addition, the resubmission has not provided any discussion around why the estimate of cyclosporin use has been sourced from all transplant patients in the ABMTRR instead of seropositive patients. The difference in proportion is small (█% compared to █%) however the value used by the resubmission is based on a patient group that does not correspond to the proposed PBS population.
- 6.64 Overall, the ESC considered that the resubmission has not provided a broad consideration of cyclosporin usage in the Australian population nor has the resubmission provided detailed consideration of the data presented, i.e. ABMTRR data from 2014 to 2016.
- 6.65 The resubmission has also maintained that the 78 day duration of treatment sourced from Trial P001 is reasonable to estimate real-world use of letermovir and that any uncertainty will be addressed in a risk share arrangement between the sponsor and Government (see 'Financial Management – Risk Sharing Arrangements' below). The ESC considered that treatment duration in practice would evolve quickly as evidence becomes available (paragraph 6.16 July 2018 PSD) and also considered that in practice nearly all patients will be treated for a period longer than 78 days (paragraph 6.45 July 2018 PSD). The 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 (paragraph 2.4 July 2018 PSD). The ESC reaffirmed the above concerns regarding treatment duration raised during the July 2018 consideration of letermovir.

6.66 The estimated number of patients, scripts and estimated net cost to the PBS/RPBS are provided in the table below.

**Table 18: Estimated use and financial implications**

|   | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6            |
|---|--------|--------|--------|--------|--------|-------------------|
| <b>Estimated extent of use</b>                        |        |        |        |        |        |                   |
| Number of patients treated                            | █      | █      | █      | █      | █      | █                 |
| July 2018 treated patients                            | █      | █      | █      | █      | █      | █                 |
| Number of scripts dispensed <sup>a</sup>              | █      | █      | █      | █      | █      | █                 |
| <b>Estimated financial implications of letermovir</b> |        |        |        |        |        |                   |
| Cost to PBS/RPBS                                      | \$ █   | \$ █   | \$ █   | \$ █   | \$ █   | \$ █              |
| Copayments  | -\$ █  | -\$ █  | -\$ █  | -\$ █  | -\$ █  | -\$ █             |
| <b>Net financial implications</b>                     |        |        |        |        |        |                   |
| Net cost to PBS/RPBS                                  | \$ █   | \$ █   | \$ █   | \$ █   | \$ █   | \$ █              |
| July 2018 overall net cost to PBS/RPBS                | \$ █   | \$ █   | \$ █   | \$ █   | \$ █   | \$ █ <sup>b</sup> |

<sup>a</sup> Assuming a weighted average of 3.27 packs per year (█% using concomitant cyclosporin and 240mg/day and █% using letermovir alone and 480mg/day).

<sup>b</sup> While the July 2018 submission did not provide estimates for Year 6 the PSCR provided an estimated net cost.

NE=not estimated

Source: Table 4-3, p102; Table 4-4, p103; Table 4-5, p105 of the resubmission and Table 12, 5.07.COM.22.

*The redacted table shows that at Year 6, the estimated number of patients was less than 10,000.*

6.67 The estimated net cost to the PBS/RPBS over the first 6 years of listing in the resubmission was \$30 to \$60 million. This was less than the \$30 to \$60 million estimated in the July 2018 submission. The key reason for the estimated decrease in net cost compared to the July 2018 estimate was the assumed lower growth rate in transplant procedures, resulting in lower eligible patient numbers, along with the assumption made by the resubmission that the first year of listing would only cover 4 months (this assumption did not correspond to the PBAC Guidelines v5.0, p107 which indicate the financial impact should be estimated over six full calendar years). If the Year 1 costs were assumed to cover an entire year and the growth rate of transplant procedures was returned to the level used in the July 2018 submission (4.58%) then the estimated net cost to the PBS/RPBS concurred with the July 2018 estimate at \$30 to \$60 million.

6.68 When the number of packs available under the requested restriction were used (4 packs) the estimated net cost over the first 6 years of listing increased to \$30 to \$60 million from the resubmission’s estimate of \$30 to \$60 million. Also including costs for the full calendar year of Year 1 increased the net costs over 6 years to \$60 to 100 million. This latter estimate was more likely to reflect the estimated net costs to the PBS/RPBS for the use of letermovir.

### **Quality Use of Medicines**

- 6.69 As in the July 2018 submission the resubmission 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.
- 6.70 DUSC highlighted (paragraph 6.59 July 2018 PSD) that educational materials and activities on drug interactions would be crucial to support appropriate use of letermovir as 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 July 2018 submission, as lower doses of letermovir were used in the drug-drug interaction studies compared with the requested listing. Section 2.7.2 of the resubmission listed drug interactions identified in the TGA's risk management plan but the ESC noted that the resubmission did not provide additional discussion of the significant drug interactions associated with co-administration of letermovir, nor did the resubmission provide discussion of educational materials and activities on drug interactions.

### **Financial Management – Risk Sharing Arrangements**

- 6.71 The resubmission stated that the sponsor is willing to enter a risk sharing arrangement with a cap/rebate structure that takes into account uncertainty associated with proportion of seropositive patients, rate of cyclosporin use and treatment duration. In regards to treatment duration the resubmission added that any uncertainty in the real-world utilisation of letermovir would be addressed through a risk-sharing arrangement such that the impact of an extended duration of use outside of the proposed estimates does not have a significant impact to the health budget.
- 6.72 The resubmission stated that the sponsor believes the risks should be shared with the Commonwealth and that any rebate payable should not exceed █%, as elements of the uncertainty being addressed are outside the control of the sponsor and are not able to be forecasted. The resubmission provided no further information on the potential risk-sharing arrangement and indicated that final details of the risk sharing arrangement would be negotiated with the Department of Health following a positive PBAC recommendation.

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

## **7 PBAC Outcomes**

- 7.1 The PBAC did not recommend the Section 100 (Highly Specialised Drugs Program) Authority Required listing for letermovir for prophylaxis of CMV infection or disease in CMV sero-positive patients who have received an allogeneic HSCT. The PBAC acknowledged the clinical utility of letermovir for this indication but considered that the mortality and re-hospitalisation benefits attributed to letermovir were not supported by the trial evidence provided in the resubmission. As these outcomes

- formed the basis of the economic model the PBAC considered that the cost-effectiveness of letermovir was unable to be assessed. The PBAC also noted that other antivirals used as prophylaxis or pre-emptive therapy were in clinical use to reduce the burden of CMV disease in this setting.
- 7.2 The PBAC noted the consumer comments and reiterated its acceptance of the clinical utility of letermovir as an orally active agent to prevent CMV infection in the post HSCT setting.
- 7.3 The PBAC recalled that in its July 2018 consideration of letermovir it had advised that both placebo and antiviral treatments would be informative comparators (paragraph 7.4 July 2018 PSD). The PBAC noted antiviral treatment was not included as a comparator in the resubmission as the sponsor argued that these agents are not routinely used in Australia for prophylaxis. The PBAC acknowledged the limitations of the ABMTRR data in providing granularity on the proportion of antiviral use that is PET versus prophylaxis for CMV. However, the PBAC considered that the data indicated antivirals continue to be used as primary prophylaxis in this context in Australia. As such the PBAC reaffirmed that, in addition to placebo, a comparison of letermovir with ganciclovir or other antivirals as prophylaxis for CMV would be informative.
- 7.4 The PBAC noted that, as with the July 2018 submission, the resubmission was based on Trial P001. The PBAC recalled that the primary outcome for this trial was clinically significant CMV infection (a composite outcome of onset of CMV end-organ disease and initiation of PET) and reaffirmed its July 2018 conclusion that the difference between letermovir and placebo for this outcome was based on the difference in PET initiation.
- 7.5 The PBAC noted that in Trial P001 a statistically significant difference between letermovir and placebo at week 48 was reported for the CMV-related mortality ( $p < 0.0001$ ) with an assumed link between CMV infection and mortality included in the economic evaluation. The PBAC noted that CMV-related mortality referred to all-cause mortality in patients who met the primary outcome of the trial. Therefore, a death in an individual with a prior CMV infection would be counted as 'CMV-related mortality' regardless of the cause of death. The PBAC agreed with the ESC that the statistically significant lower rate of CMV-related mortality in the letermovir group was not meaningful because it may not reflect a difference in mortality attributable to letermovir treatment. In addition, the PBAC agreed with the ESC that the post-hoc analysis of all-cause mortality in patients with and without clinically significant CMV infection did not demonstrate that letermovir is an effect modifier for the effect of CMV infection on mortality, as claimed by the resubmission and PSCR.
- 7.6 The PBAC noted that the sponsor highlighted in the pre-PBAC response the challenges associated with undertaking a study that is adequately powered to detect a mortality benefit in allogeneic HSCT patients, especially when utilising the surrogate endpoint of CMV infection which is known to increase the risk of mortality. However, the PBAC disagreed with the sponsor and considered that based on the size of the modelled mortality benefit that Trial P001 appeared to be adequately powered to detect such a

difference.

- 7.7 The resubmission cited an advantage in re-hospitalisation for patients with clinically significant CMV infection. However, the PBAC agreed with the ESC that when discontinued and missing patients were excluded from the comparison, the proportion re-hospitalised was similar between the letermovir and placebo groups. In addition, the PBAC noted that no differences in the occurrence of bacterial and/or fungal infections were evident between letermovir-treated and placebo-treated patients in Trial P001.
- 7.8 The PBAC concluded that, given the trial evidence did not demonstrate a difference in mortality attributable to letermovir treatment, and there appeared to be no difference in re-hospitalisations or the occurrence of bacterial or fungal infections between letermovir and placebo-treated patients, the advantage for letermovir remained largely based on a reduction in the use of PET.
- 7.9 The PBAC noted the Gagelmann 2018 meta-analysis of comparative efficacy and safety of different antiviral agents for CMV prophylaxis in allogeneic HSCT. The PBAC acknowledged the limitations of the meta-analysis and network meta-analysis and considered that the overall analysis suggested that there was probably little or no difference in the effect of letermovir in preventing CMV disease compared with other antivirals.
- 7.10 The PBAC reaffirmed its July 2018 recommendation that the claim of non-inferior safety compared to placebo was appropriate. The PBAC recalled that there are well known toxicities (e.g. bone marrow suppression) associated with currently used antiviral treatments and acknowledged that letermovir was less toxic than existing antiviral agents.
- 7.11 The PBAC recalled that in July 2018 it had recommended that the modelled economic analysis should be based on the health benefits demonstrated in the trial, i.e. reduction in the use of PET (paragraph 7.8 July 2018 PSD). The PBAC noted that the resubmission did not adopt this recommended approach and instead based the revised economic model on CMV infection and mortality outcomes, along with the re-hospitalisation outcomes. The PBAC noted that the assumed link between CMV infection and mortality was a key driver of the economic model. As outlined above the PBAC considered that the trial evidence did not support the claimed link between letermovir treatment, CMV infection and the modelled clinical outcomes. In addition, the PBAC considered the assumption of 78 days of letermovir treatment was likely underestimated and hence the cost of letermovir in the economic model may not reflect the cost associated with potential use in practice. The PBAC concluded that the economic evaluation presented in the resubmission was flawed and did not provide a reliable estimate of the cost-effectiveness of letermovir.
- 7.12 The PBAC considered that the financial estimates reported in the resubmission remained uncertain.
- 7.13 The PBAC proposed that any future resubmission should be a major submission. The

PBAC considered that such a resubmission should revise the economic model to be based on the health benefits demonstrated in the trial, i.e. reduction in the use of PET. In addition, the PBAC considered the model should incorporate cost offsets arising from the increased PET requirement with placebo and the health gains associated with the reduction in use of PET with letermovir. The PBAC considered that based on the information available a substantial reduction in price would be required to render letermovir cost-effective for the indication sought for listing. The PBAC advised that a comparison of letermovir with antivirals as prophylaxis for CMV should be included in any future resubmission to allow the incremental clinical and cost-effectiveness of letermovir over the use of antivirals in the context to be evaluated.

7.14 The PBAC noted that this resubmission 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 had no comment.