# 5.10 MARIBAVIR, Tablet 200 mg, Livtencity®, Takeda Pharmaceuticals Australia Pty Ltd

## 1 Purpose of submission

1.1 The Category 1 submission requested Section 100, Highly Specialised Drugs Program listing for maribavir for the treatment of post-transplant cytomegalovirus (CMV) infection and disease resistant, refractory or intolerant to one or more prior therapies.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus the current standard of care, stated to be oral valganciclovir, IV ganciclovir, IV foscarnet and/or IV cidofovir.

**Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)**

| Component | Description |
|---|---|
| Population | Adults with post-transplant (HSCT and SOT) CMV infection and disease resistant, refractory, or intolerant to one or more prior therapies |
| Intervention | Maribavir 400 mg (two 200 mg tablets) twice daily (total daily dose 800 mg) |
| Comparator | Current standard of care which includes:<br>• Ganciclovir<br>• Valganciclovir<br>• Foscarnet<br>• Cidofovir |
| Outcomes | • CMV viraemia clearance (<137 IU/mL)<br>• Symptom control (resolution/improvement of CMV disease/syndrome or absence of the development of CMV disease/syndrome)<br>• Treatment-emergent adverse events<br>• Treatment-emergent adverse events leading to discontinuation<br>• Health-related quality of life<br>• Maribavir resistance profile<br>• Mortality |
| Clinical claim | Maribavir is more effective and safer than current standard of care (ganciclovir, valganciclovir, foscarnet and cidofovir) in adults with post-transplant CMV infection and disease resistant, refractory, or intolerant to one or more prior therapies. |

Source: Table 1.1.1, p 21 of the submission.
CMV = cytomegalovirus; HSCT = haematopoietic stem cell transplant; IU = international unit; SOT = solid organ transplant

## 2 Background

### *Registration status*

2.1 Maribavir was TGA registered on 7 October 2022 for the treatment of post-transplant cytomegalovirus (CMV) infection and disease refractory, resistant or intolerant to one or more prior therapies.

2.2 The indication approved by the US FDA is more restrictive: post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir or foscarnet[1].

2.3 The indication approved by the European Medicines Agency is also more restrictive: cytomegalovirus (CMV) infection and/or disease that are refractory (with or without resistance) to one or more prior therapies, including ganciclovir, valganciclovir, cidofovir or foscarnet in adult patients who have undergone a haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT)[2].

# 3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

| **MEDICINAL PRODUCT**<br>**medicinal product pack** | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№.of Rpts** | **Available brands** |
|---|---|---|---|---|---|
| *MARIBAVIR* | | | | | |
| ~~Maribavir, 200mg oral film coated tablets, 28 tablet bottle~~<br>*maribavir 200 mg tablet, 28* | NEW | 4 | 112 | 1 | Livtencity |
| ***Category / Program:*** *Section 100 – Highly Specialised Drugs Program (Public/Private/Community Access (CA))* | | | | | |
| ***Prescriber type:*** ☒*Medical Practitioners* | | | | | |
| ***Restriction type:***<br>☒*Authority Required (Streamlined)* | | | | | |
| ***Administrative Advice:*** *Special Pricing Arrangements apply.* | | | | | |
| ***Administrative Advice:*** *No increase in the maximum number of repeats may be authorised.* | | | | | |
| ~~**Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.~~ | | | | | |
| ~~**Treatment phase:** Initial treatment~~ | | | | | |
| **Condition:** Post-transplant cytomegalovirus (CMV) infection and disease | | | | | |
| **Indication:** Acute treatment of adults with post-transplant cytomegalovirus (CMV) infection *or CMV* disease resistant, refractory or intolerant to one or more prior therapies | | | | | |
| **Clinical criteria:** | | | | | |
| Patient must have received a hematopoietic stem-cell transplant | | | | | |
| OR | | | | | |
| Patient must have received a solid-organ transplant | | | | | |
| AND | | | | | |
| Patient must have a CMV infection or *CMV* disease that is resistant, refractory or intolerant to one or more prior anti-CMV therapies | | | | | |
| **Population criteria:** | | | | | |
| Patient must be ≥18 years old *or older* | | | | | |
| **Prescribing instructions:** | | | | | |

[1] https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215596lbl.pdf (accessed 16 July, 2023).
[2] https://www.ema.europa.eu/en/documents/product-information/livtencity-epar-product-information_en.pdf (accessed 16 July, 2023).

| |
|---|
| Patients are determined to be refractory if after two weeks of appropriately dose*d* antiviral therapy their peak viral load has decreased by ~~<~~ *less than* 1 log10~~10~~ versus baseline. |
| Patients are determined to be resistant by the identification of a viral genetic alteration that decreases susceptibility to one or more antiviral drugs. |
| Patients are determined to be intolerant if the potential toxicity of one or more antivirals prevents their appropriate use. |
| Maribavir should be used as monotherapy and use with valganciclovir or ganciclovir is contraindicated |

| |
|---|
| ~~**Treatment phase:** Continuing treatment~~ |
| ~~**Condition:** Post-transplant cytomegalovirus (CMV) infection and disease~~ |
| ~~**Indication:** Acute treatment of adults with post-transplant cytomegalovirus (CMV) infection and disease resistant, refractory or intolerant to one or more prior therapies~~ |
| ~~**Clinical criteria:**~~ |
| ~~Patient must have previously received PBS-subsidised treatment with this drug for this condition~~ |
| ~~**Population criteria:**~~ |
| ~~Patient must be ≥18 years old~~ |
| ~~**Prescribing instructions:**~~ |
| ~~Maribavir should be used as monotherapy and use with valganciclovir or ganciclovir is contraindicated~~ |

3.2 The submission's proposed restriction does not align with the population studied in the SOLSTICE trial. Eligibility for the trial required infection refractory to treatment. Patients with resistance alone, or intolerance alone, were not eligible. The Pre-Sub-Committee Response (PSCR) stated the SOLSTICE trial excluded patients who had genotypic resistance to investigator assigned anti-CMV treatment (IAT) but who were not refractory because in this scenario, the IAT was expected to be ineffective. The PSCR argued that patients with resistance alone should not be excluded from receiving maribavir. The ESC noted that in Australian clinical practice genotypic testing for resistance is not available within useful timeframes, therefore clinical decisions are likely to be based on response to treatment rather than genotypic testing for mutations conferring resistance.

3.3 The evaluation highlighted that the difference in outcomes in favour of maribavir in the SOLSTICE trial was large in patients refractory **and** resistant, but smaller in patients refractory **but not** resistant. However, as noted above, results of genotypic testing are not available in a clinically useful timeframe, and ESC considered that accordingly, it would not be appropriate for the restriction to stipulate that the infecting CMV must have genotypic resistance to ganciclovir/valganciclovir.

3.4 The wording of the proposed restriction was unclear in relation to intolerance. The indication requires that the patient be "intolerant to one or more prior therapies", implying that there must have been intolerance. However, the Prescribing Instructions state that "Patients are determined to be intolerant if the **potential** toxicity of one or more antivirals prevents their appropriate use" [emphasis added], which suggests that concern about possible toxicity is sufficient. The ESC considered that intolerance would imply prior use of the therapy. The PSCR stated that intolerance is an approved reason for treatment within the TGA indication, and a criterion based on potential toxicity (e.g., ganciclovir haematological toxicity in haematopoietic stem cell

transplant patients or foscarnet nephrotoxicity in renal transplant patients i.e., contraindication rather than intolerance) may be appropriate.

3.5 The ESC considered that it may be appropriate to align the restriction with the trial criteria such that patients must have received at least two weeks treatment with ganciclovir or valganciclovir for this infection, with virological or clinical failure.

3.6 No evidence to support the use of maintenance treatment beyond 8 weeks of treatment with maribavir, or of repeated courses for recurrent infections, was presented. The PSCR stated that the National Institute for Health and Care Excellence (NICE) did not restrict use of maribavir to 8 weeks in their recommendation for listing, and that use beyond 8 weeks should only be for individual circumstances where there is ongoing CMV viraemia, since this is a predictor of recurrence and the development of resistant mutations. The ESC noted that development of resistance to maribavir during treatment can occur, and suggested that as such, it may be appropriate to restrict treatment with maribavir to 8 weeks. The ESC noted that such a restriction would be in line with the trial evidence submitted, where patients were only able to receive up to 8 weeks of treatment with maribavir.

3.7 The ESC considered it may also be appropriate for the restriction to remain silent regarding age as there is no reason to assume treatment efficacy would be different in patients aged <18 years.

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

# 4 Population and disease

4.1 CMV is a common infection. The virus is present in body fluids, including saliva, and infection is usually transmitted by close contact, especially with children, who may shed virus for prolonged periods after infection. Infection most commonly occurs in childhood, with about 50% of young adults in high-income countries being seropositive, but can occur at any age. After initial infection, latent infection is lifelong. Primary infection is most often asymptomatic, and even if symptomatic immunocompetent individuals rarely become seriously ill. CMV may cause serious illness in immunosuppressed individuals, by reactivation of latent infection, or by primary infection of those not previously exposed to CMV. Infection may be acquired in the usual way, by close contact with an infected person, or by receiving a solid organ or haematopoietic stem cell transplant from a person with latent CMV infection.

4.2 A transplant recipient may, therefore, have no CMV infection, latent infection, active infection with viral replication but no symptoms, or CMV disease.

4.3 Transplant recipients believed to have latent CMV infection, or to be at high risk of infection (e.g., parents of small children) are commonly given "prophylactic

treatment". Maribavir has been trialled for use as prophylactic treatment but was found to be ineffective[3].

4.4 Transplant recipients with active CMV infection, defined as viral replication with isolation of CMV DNA from body fluid or tissue, but who do not have CMV disease, are commonly given "pre-emptive treatment". This practice is not based on robust evidence, and although the risk of CMV disease is higher in those with higher levels of CMV replication, the level of CMV replication at which treatment is beneficial is not well-defined. If treatment is given, it is continued for at least two weeks and until CMV DNA is no longer detectable in blood or plasma.

4.5 CMV disease in an immuno-suppressed person, whether due to reactivation of latent infection, or to primary infection, or infection acquired by transplantation, can manifest as a syndrome of fever, malaise, leukopenia and atypical lymphocytosis, or as tissue-invasive disease, commonly affecting the liver, lung, retina, brain and meninges, or colon. Immuno-suppressed patients with CMV disease require treatment.

4.6 The submission proposed listing of maribavir for pre-emptive treatment and treatment for CMV disease, but not prophylactic treatment.

4.7 Current treatment options for pre-emptive treatment of asymptomatic CMV infection, and for treatment of CMV disease are ganciclovir and its prodrug valganciclovir, foscarnet, and cidofovir.

4.8 All four drugs act by inhibiting the viral DNA polymerase, encoded by the viral gene UL54. Ganciclovir must be phosphorylated by a phosphotransferase encoded by the viral gene UL97 before it can inhibit the DNA polymerase.

4.9 Some strains of CMV have mutations in UL54 and or UL97 associated with drug resistance, but the presence of mutations associated with resistance to a drug does not preclude therapeutic success with it, and therapeutic failure can occur without mutations known to confer resistance.

4.10 The commonest resistance mutations are in UL97; they confer varying degrees of resistance to ganciclovir but not to foscarnet or cidofovir. Mutations in UL54 confer varying degrees of resistance to various combinations of ganciclovir, foscarnet and cidofovir. Some CMV strains have mutations in both UL97 and UL54, and these strains have high-level resistance to ganciclovir.

4.11 Maribavir acts by inhibiting the viral phosphotransferase encoded by UL97. (For this reason, co-administration with ganciclovir and valganciclovir is contra-indicated). UL97 mutations different to those common in ganciclovir-resistant strains confer

[3] Marty FM, Ljungman P, Papanicolaou G, et al. Maribavir prophylaxis for prevention of cytomegalovirus disease in recipients of allogeneic stem-cell transplants: A phase 3, double-blind, placebo-controlled, randomised trial. *Lancet Inf Dis* 2011; 11:284-292.

resistance to maribavir, either alone or together with ganciclovir. Some mutations in the CMV gene UL27 also confer maribavir resistance, but the function of the protein encoded by UL27 is not well understood.

4.12 Maribavir does not cross the blood-brain barrier and is not used for CMV retinitis or meningo-encephalitis.

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

# 5 Comparator

5.1 The submission nominated 'standard medical management' as the main comparator, consisting of ganciclovir, valganciclovir, foscarnet, cidofovir, alone or in combination (foscarnet and cidofovir cannot be given together because of renal toxicity). The main argument provided in support of this nomination was that all four products are currently used to treat CMV infection in the target population, although treatment choices vary among centres. The TGA Indications and PBS listings for these four products are shown in Table 2.

**Table 2: TGA indications and PBS listings for comparators**

| Product | TGA indication | PBS listing |
|---|---|---|
| Ganciclovir | • Prophylaxis of CMV in SOT and BMT recipients at risk of CMV disease.<br>• Palliative treatment of confirmed sight-threatening CMV disease in AIDS and other severely immunocompromised individuals.<br>• Treatment of confirmed CMV pneumonitis in BMT recipients. | • Prophylaxis of CMV in BMT and SOT patients.<br>• Treatment of CMV retinitis in severely immunocompromised patients including HIV. |
| Valganciclovir | • Treatment of CMV retinitis in adult patients with AIDS.<br>• Prophylaxis of CMV disease in adult and paediatric SOT patients who are at risk. | • Treatment of CMV retinitis in patients with HIV.<br>• Prophylaxis of CMV in patients with SOT at risk of CMV disease. |
| Foscarnet | • Treatment of CMV retinitis in patients with AIDS.<br>• Treatment of aciclovir resistant herpes simplex virus (HSV) infections (defined by clinical trial or in vitro resistance) in immunocompromised patients with human immunodeficiency virus (HIV) infection. | Not listed |
| Cidofovir | • Treatment of CMV retinitis in patients with AIDS. | Not listed |

Source: Table 1.1.5, p32-33 of the submission and product information documents.
AIDS = acquired immunodeficiency syndrome; BMT = bone marrow transplant; CMV = cytomegalovirus; SOT = solid organ transplant

5.2 The ESC noted that none of the nominated comparators are listed on the PBS for the requested patient population, but considered it was likely that use of valganciclovir and ganciclovir on the PBS extended to patients who required CMV treatment. The ESC considered that patients would likely commence treatment in an inpatient setting, and therefore it would be difficult to determine proportionate use of the potential comparators in the PBS setting.

5.3 The evaluation considered that foscarnet or cidofovir would be the comparators of choice should maribavir be restricted to second line use and that patients who could not tolerate second-line therapy (e.g., due to poor kidney function) would continue to

be treated with valganciclovir or ganciclovir despite their poor response. The PSCR stated that the SOLSTICE trial was designed to capture this dynamic, since it reflects current clinical practice.

5.4 The ESC considered that while the most likely comparator is foscarnet, in clinical practice patients not responding to first-line treatment with valganciclovir or ganciclovir may be re-treated with higher doses of these therapies, therefore higher doses of these therapies should also be considered as comparators.

5.5 The evaluation considered that a comparison with foscarnet is difficult because the SOLSTICE trial did not report outcomes according to the type of IAT as a pre-specified analysis, and that only a few patients in SOLSTICE received cidofovir. The PSCR provided a post-hoc responder analysis of the primary outcome by IAT treatment (see 6.33).

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

# 6 Consideration of the evidence

## *Sponsor hearing*

6.1 The sponsor requested a hearing for this item. The clinician discussed how maribavir would be used in practice, and noted that ganciclovir and valganciclovir are used as initial treatment, which would be expected to continue. The clinician noted that second line treatment, foscarnet, is quite toxic, relatively expensive, and requires patients to be hospitalised for IV administration. The clinician considered that maribavir would therefore be preferred over foscarnet if treatment with ganciclovir or valganciclovir is not effective. The PBAC also noted that the clinician addressed other matters in response to the Committee's questions and the Committee considered the sponsor hearing to be informative.

## *Consumer comments*

6.2 The PBAC noted and welcomed the input from health care professionals (2) via the Consumer Comments facility on the PBS website. The comments described the impact of CMV infection for transplant recipients as having high morbidity, graft failure and mortality. The comments also discussed a range of benefits of treatment with maribavir, including fewer side effects and oral administration, and noted that there are limited treatment options available for patients with post-transplant CMV infection.

## *Clinical trial*

6.3 The submission was based on the SOLSTICE trial comparing maribavir to the treating clinician's choice of anti-CMV treatment in patients refractory to their current treatment. Details of the trial presented in the submission are provided in Table 3.

**Table 3: Trials and associated reports presented in the submission**

| Trial ID | Protocol title/ Publication title | Publication citation |
|---|---|---|
| NCT 02931539 | SOLSTICE Clinical Study Report: A Phase 3, Multicenter, Randomized, Open-label, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Treatment Compared to Investigator-assigned Treatment in Transplant Recipients with Cytomegalovirus (CMV) Infections that are Refractory or Resistant to Treatment with Ganciclovir, Valganciclovir, Foscarnet, or Cidofovir<br>Avery RK, Alain S, Alexander BD, et al. Maribavir for refractory cytomegalovirus infections with or without resistance post-transplant: Results from a Phase 3 randomized clinical trial.<br><br>Plus 13 abstract citations for the same trial | February 2021<br><br>2022; 75(4):690-701 |

Source: Table 2.2.2, pp 48-49 of the submission.

6.4 The key features of the direct randomised trial are summarised in Table 4.

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

| Trial | N | Design/ duration | Risk of bias | Patient population | Outcome(s) | Use in modelled evaluation |
|---|---|---|---|---|---|---|
| Maribavir vs. investigator assigned treatment (ganciclovir, valganciclovir, foscarnet, cidofovir combination) | | | | | | |
| SOLSTICE | 352 | R, 2:1 maribavir or IAT, OL, MC<br>8 week + 12 week follow-up | High | ≥ 12 years[a], HSCT or SOT, CMV infections refractory to one or more of ganciclovir, valganciclovir, foscarnet, or cidofovir, including CMV infections with confirmed resistance to one or more anti-CMV agents. | CMV viraemia clearance at 8 week, control of CMV disease, recurrence | Used in stage 1 of the model to inform clearance, recurrence and mortality transitions |

Source: Pp 51, 57 of the submission.

CMV = cytomegalovirus; HSCT = haemopoietic stem cell transplant; IAT = investigator assigned treatment; MC = multi-centre; OL = open label; R = randomised; SOT = solid organ transplant

[a] No patients under age 18 were enrolled.

6.5 Details of trials excluded by the submission but considered relevant are shown in Table 5.

**Table 5: Excluded trials with relevant results**

| Trial | N | Design and duration | Patient population | Primary outcome |
|---|---|---|---|---|
| NCT02927067 | 553 | R, DB, DD, maribavir 400 mg bd or valganciclovir 900 mg bd, 8 wk | HSCT, ≥ 16 yrs, CMV infection, no CMV organ disease, first episode of CMV after transplant, no resistance to ganciclovir | CMV viraemia clearance at 8 wk (same definition of clearance as SOLSTICE) |
| Maertens et al NEJM 2019; 381:1136-47 | 161 | R, OL to maribavir versus valganciclovir but blinded to maribavir dose; maribavir 400 mg bd, 800 mg bd, 1200 mg bd or valganciclovir, 12 wk | HSCT or SOT, ≥ 18 yrs, CMV DNA 1,000 to 100,000 IU/mL, no CMV organ disease, no resistance to ganciclovir | CMV viraemia clearance at 3 or 6 wk (same definition of clearance as SOLSTICE) |

Source: constructed during the evaluation from: https://clinicaltrials.gov/study/NCT02927067 (accessed 15 July, 2023); Maertens 2019[4].
bd = twice daily; CMV = cytomegalovirus; DB = double blind; DD = double dummy; HSCT = haemopoietic stem cell transplant; OL = open label; R = randomised; SOT = solid organ transplant; wk = week; yrs = years

6.6 To be included in the SOLSTICE trial, patients were required to be refractory to the most recently used anti-CMV agent, defined as failure to achieve >1 $\log_{10}$ decrease in CMV DNA level in whole blood or plasma after a 14-day or longer treatment period (i.e., there was no upper limit to allowable treatment duration, and the median duration of infection before trial enrolment was more than 5 weeks – see Table 7, below). Patients with genotypic resistance or prior intolerance had to meet the criteria for refractoriness (i.e., resistance and intolerance were ignored for eligibility).

6.7 About two-thirds of patients were eligible on the basis of refractoriness to ganciclovir/valganciclovir (SOLSTICE CSR, p141). This is similar to the proportion of patients experiencing their first post-transplant CMV infection, consistent with the use of ganciclovir/valganciclovir as first-line treatment. The other third must have been eligible on the basis of refractoriness to foscarnet or cidofovir, but the proportions of each are not given in the CSR. The importance of this is that, assuming standard treatment guidelines were followed, the use of foscarnet or cidofovir would imply that the patients had previously failed treatment with or were infected with CMV resistant to ganciclovir /valganciclovir, although this also was not reported in the CSR. Therefore, it seems likely that all patients in the trial had, or had a history of, CMV infection refractory or resistant to ganciclovir/valganciclovir.

6.8 Patients enrolled in SOLSTICE were randomised 2:1 to maribavir or investigator assigned treatment (IAT). Randomisation was stratified by transplant type (haematopoietic stem cell vs solid organ), and by high (≥ 91,000 IU/mL in plasma), medium (≥ 9,100 and < 91,000 IU/mL in plasma) and low (≥ 910 and < 9,100 IU/mL in plasma) CMV DNA. Patients received maribavir 400 mg twice daily or IAT for 8 weeks. After the 8-week treatment period patients were followed-up off treatment for 12 weeks (total 20 weeks).

[4] Maertens J, Cordonnier C, Jaksch P, Poire X et al. Maribavir for preemptive treatment of cytomegalovirus reactivation. *NEJM* 2019; 381(12):1136-1147.

6.9 Patients randomised to IAT had their treatment chosen at the discretion of the local investigator from among the four drugs allowed: ganciclovir, valganciclovir, foscarnet and cidofovir. Although treatment failure with the current treatment was an entry criterion, patients could continue their current treatment unchanged, receive the same agent at a higher dose or reduced dosing interval, change to another agent, or receive a combination of two agents (but not foscarnet + cidofovir). Dose and dosing interval could be changed during treatment, but a change to another agent (except switching between ganciclovir and valganciclovir and vice versa), or addition of an agent not chosen at randomisation was considered treatment failure.

6.10 The IAT chosen was ganciclovir for 28 (24.1%) of patients, valganciclovir for 28 (24.1%), foscarnet for 47 (40.5%), cidofovir for 6 (5.2%), and foscarnet + ganciclovir/valganciclovir for 7 (6.0%).

6.11 Of 69 patients with CMV resistant to ganciclovir/valganciclovir at baseline randomised to IAT, 32 (46.4%) were treated with ganciclovir/valganciclovir, so that of 56 patients treated with ganciclovir/valganciclovir most (57.1%) were known to have CMV resistant to that treatment. Of 7 patients with CMV resistant to foscarnet at baseline, none received foscarnet as IAT; of 14 patients with CMV resistant to cidofovir at baseline, one received cidofovir as IAT (SOLSTICE CSR, Table 18, p139; SOLSTICE CSR, Table 17, p138). The PSCR stated that clinicians were able to assign the most appropriate treatment in the IAT comparator arm to ensure that patients received the best care, aligned with how clinicians currently treat their patients. The PSCR also stated that resistance can be low, medium or high, and if it is lower the ganciclovir dose can be increased to manage resistance. The ESC considered that this was consistent with clinical practice and with the inclusion of ganciclovir/valganciclovir (at higher doses) as relevant comparators.

6.12 It is possible that some or all of the patients treated with ganciclovir despite known resistance, or the patient treated with cidofovir despite known resistance, could not receive either of the other drugs because of toxicity (eligibility required only that the investigator was willing to use at least one of the allowed agents). This was not reported in the CSR, however.

6.13 The primary outcome, clearance of plasma CMV DNA at the end of Study Week 8, was defined as plasma CMV DNA concentrations below the lower limit of quantification (i.e., <137 IU/mL) in 2 consecutive samples separated by at least five days, regardless of whether study-assigned treatment was discontinued before the end of 8 weeks. The planned times for evaluation of viral load were Weeks 7 and 8, but data from adjacent weeks may have been used to impute missing data. Subjects who received non-randomised anti-CMV treatment were considered as non-responders.

6.14 A pre-specified "key secondary" outcome was CMV viraemia clearance and resolution or improvement of tissue-invasive CMV disease or CMV syndrome for subjects symptomatic at baseline, or viraemia clearance and no symptoms of tissue-invasive CMV disease or CMV syndrome for subjects asymptomatic at baseline at the end of

8 weeks and maintenance of this treatment effect for an additional 8 weeks off treatment.

6.15 CMV viraemia clearance according to preceding anti-CMV treatment, to the IAT chosen, or according to genotypic resistance, were not pre-specified outcomes.

6.16 Recurrence of CMV viraemia was defined as plasma CMV DNA concentrations at or above the lower limit of quantitation (≥137 IU/mL), in two consecutive plasma samples separated by at least five days, at any time after achieving viraemia clearance. For assessing recurrence, CMV DNA measurements were counted whether or not non-randomised treatment was being given.

6.17 Patients randomised to IAT who had received at least three weeks of treatment could be switched to maribavir ("the maribavir rescue arm"), if they met any of the following criteria:

- rising CMV viraemia $\geq$ 1 $\log_{10}$ from baseline;
- tissue-invasive CMV had not improved or worsened if it was present at baseline, or had appeared in subjects asymptomatic at baseline, and CMV viraemia had decreased by < 1 $\log_{10}$ from baseline;
- CMV viraemia clearance had not been achieved and continued anti-CMV treatment was considered to be necessary and there was intolerance to the IAT (at least 50% increase in serum creatinine or haemorrhagic cystitis if treated with foscarnet or cidofovir or neutrophil count < 0.5 x $10^9$/L if treated with ganciclovir or valganciclovir).

6.18 Intolerance to the IAT alone, lack of clinical response alone, or intolerance plus lack of a clinical response, did **not** allow entry to the maribavir rescue arm. Twenty-two patients were accepted into the rescue arm; they received maribavir 400 mg twice daily for 8 weeks, followed by 12 weeks follow-up. Their data were recorded separately, but they were otherwise handled in the same way as patients randomised to maribavir. Patients who could not continue their IAT but were not eligible for the maribavir rescue arm "were treated as deemed appropriate by the investigator" (SOLSTICE CSR, p46); whether this could have included maribavir was not stated.

6.19 The evaluation noted the option of switching to maribavir within the trial may have encouraged the enrolment of patients whose current treatment was failing in order to provide access to maribavir. If this was the case, the results of the trial are subject to a high risk of bias. The existence of bias is suggested by the observation that the proportions of patients completing 8 weeks treatment, and completing the 20 week treatment + follow-up period, were higher in patients in the maribavir rescue arm than in patients randomised to maribavir (see Table 6). The PSCR stated that the inclusion of rescue arm was ethically necessary and needed to reflect clinical practice where clinicians will change treatment in the case of treatment failure, and that it would be "highly questionable for a clinician to treat a post-transplant CMV infection with IAT that is failing, to gain access to maribavir. Especially given patients were required to

be treated with IAT and then either have increasing viral load, worsening symptoms, or significant intolerance, combined with a substandard response that required ongoing treatment".

6.20 The flow of patients through SOLSTICE is shown in Table 6.

**Table 6: Disposition of patients in SOLSTICE**

| | Maribavir N = 235 | IAT N = 117 |
|---|---|---|
| Completed 8 weeks on treatment, n (%) | 183 (77.9%) | 37 (31.6%) |
| Discontinued treatment before 8 weeks, n (%) | 51 (21.7%) | 79 (65.7%) |
| Withdrawn consent | 2 (0.9%) | 8 (6.8%) |
| Adverse event | 15 (6.4%) | 36 (30.8%) |
| Lack of efficacy | 21 (8.9%) | 16 (13.7%) |
| Death | 14 (6.0%) | 5 (4.3%) |
| Completed study to 20 week, n (%) | 199 (84.7%) | 58 (48.6%) |
| Discontinued study before 20 week, n (%) | 36 (15.3%) | 37 (31.6%) |
| Withdrawn consent | 8 (3.4%) | 16 (13.7%) |
| Adverse event | 1 (0.4%) | 5 (4.3%) |
| Noncompliance | 0 | 6 (5.1%) |
| Death[c] | 25 (10.7%) | 11 (9.5%) |
| **Maribavir rescue arm** | | |
| Entered maribavir rescue arm, n/N (%) | | 22/51 (43.1%) |
| Completed 8-week rescue treatment, n/N (%) | NA | 21/22 (95.4%)[a] |
| Completed rescue arm to 20-week, n/N (%) | | 20/22 (90.9%)[b] |

Source: SOLSTICE CSR, Figure 2, p124, except for data for deaths which are from Table 42, pp229-230.
IAT = investigator assigned treatment; NA = not applicable
[a] One subject was withdrawn from rescue maribavir by the sponsor.
[b] One subject was hospitalised in another city and could not complete study follow-up visits.
[c] Two patients in each group died after the end of the 20-week treatment + follow-up period due to events emerging before the end of 20 weeks.

6.21 The PSCR stated that an open-label design was the only ethical and feasible way to conduct the study and that enabling physicians to choose appropriate IAT for patients was specifically aimed at limiting the impact of the adverse events on the patient's ability to complete their course of therapy. The PSCR stated that the primary outcome of viraemia clearance was assessed in a blinded fashion. The ESC considered the SOLSTICE trial to have a high risk of bias, and commented that the high rate of discontinuations in patients prior to 8 weeks in the IAT comparator arm confounded the trial results and introduced significant uncertainty. The pre-PBAC Response stated that the high discontinuation rate from the IAT arm occurred as a direct result of the challenges with the available antivirals, in that the toxicity of IAT led to higher discontinuation due to treatment-emergent adverse events in the IAT group than in the maribavir group.

6.22 Baseline characteristics are shown in Table 7.

**Table 7: Baseline characteristics of patients participating in SOLSTICE**

| | Maribavir N = 235 | IAT N = 117 |
|---|---|---|
| Age, years<br>Median (range) | 57 (19-79) | 54 (19-77) |
| Age ≥ 65, n (%) | 54 (23%) | 16 (13.7%) |
| Male, n (%) | 148 (63%) | 65 (55.6%) |
| Solid organ transplant | 142 (60.4%) | 69 (59.0%) |
| Haematopoietic stem cell transplant[a] | 93 (39.6%) | 48 (41.0%) |
| Baseline plasma CMV DNA[b] IU/mL, mean (SD) | 52,921.6 (335,894.7) | 88,171.8 (595,022.2) |
| Baseline plasma CMV DNA[b] IU/mL, n (%)<br><9100<br>≥ 9100 and < 91,000<br>≥ 91,000 | <br>108 (46.0%)<br>99 (42.1%)<br>28 (11.9%) | <br>54 (46.2%)<br>49 (41.9%)<br>14 (12.0%) |
| CMV clinical status, n (%)<br>CMV syndrome<br>Tissue-invasive disease<br>Asymptomatic infection | <br>16 (6.8%)<br>18 (7.7%)<br>201 (85.5%) | <br>10 (8.5%)<br>4 (3.4%)<br>103 (88.0%) |
| Time from first CMV positive testing for current infection to first dose of study treatment, days<br>Mean (SD)<br>Median<br>Q1, Q3 (range) | <br>70.5 (85.5)<br>38.0<br>23, 93 (3 – 716) | <br>63.54 (58.2)<br>40.0<br>25, 79 (3 – 312) |
| CMV RAS conferring resistance to ganciclovir, foscarnet or cidofovir at baseline, n (%) | 121 (51.7%) | 69 (59.5%) |
| CMV RAS conferring resistance to maribavir at baseline, n (%) | 1 (0.4%) | 3 (2.6%) |

Source: Table 2.4.2, p63; Table 2.4.3, p65 of the submission.
CMV = cytomegalovirus; IAT = investigator assigned treatment; IU = international units; RAS = resistance-associated amino acid substitution; SD = standard deviation.
[a] 92/93 patients randomised to maribavir and 48/48 randomised to IAT had received allogenic HSCT.
[b] Measured values for CMV DNA are of the order of three-fold higher in blood than in plasma.

6.23 Baseline characteristics were similar in the maribavir and IAT groups, except that there was a higher proportion of patients aged over 65 years in the maribavir-treated group.

6.24 A large majority of patients in the trial had asymptomatic infection, despite the infection having been present for some time at enrolment, and relatively few had high levels of CMV DNA in plasma.

## *Comparative effectiveness*

6.25 The outcomes of the SOLSTICE trial are summarised in Table 8.

**Table 8: Summary of outcomes in SOLSTICE**

| | Maribavir N = 235 | IAT N = 117 | Adjusted difference in proportion responding (95% CI)[a] | HR (95% CI) |
|---|---|---|---|---|
| **CMV viraemia clearance at 8 week** | | | | |
| n (%) | 131 (55.7%) | 28 (23.9%) | **32.8 (22.8, 42.7)** | NR |
| **CMV viraemia clearance at any time during 8 wk treatment period** | | | | |
| n (%) | 174 (74.0%) | 61 (52.1%) | **23.6 (13.2, 33.9)** | NR |
| **CMV viraemia clearance and symptom resolution or no new symptoms at 8 week and 16 week** | | | | |
| n (%) | 44 (18.7%) | 12 (10.3%) | **9.5 (2.0, 16.9)** | NR |
| **Improvement or resolution of symptoms of CMV disease at week 8 in patients with symptoms at baseline** | | | | |
| n/N (%) | 16/21 (76.2%) | 5/8 (62.1%) | NR | NR |
| **New onset symptomatic CMV disease to week 20 in patients asymptomatic at baseline** | | | | |
| n (%) | 14 (6.0%) | 7 (6.0%) | NR | NR |
| **Recurrence of CMV viraemia after clearance** | | | | |
| During 8 week treatment period, n/N (%)[b] | 33/174 (19.0%) | 8/61 (13.1%) | NR | NR |
| After 8 week treatment period, n/N (%)[b] | 71/184 (38.6%) | 14/65 (21.5%) | NR | NR |
| **CMV viraemia clearance at 8 week by baseline resistance to ganciclovir, foscarnet, or cidofovir** | | | | |
| Patients with resistant CMV responding, n/N (%) | 76/121 (62.8%) | 14/69 (20.3%) | NR | NR |
| Patients without resistant CMV responding, n/N (%) | 42/96 (43.8%) | 11/34 (32.4%) | NR | NR |
| **CMV viraemia clearance at 8 week when maribavir RAS developed on treatment** | | | | |
| Patients responding, n/N (%), | 1/42 (2.4%) | NA | NA | NA |

Source: SOLSTICE CSR, Table 22, p149; Table 23, p151; Table 28, p162; p164; pp172-173; Table 30, p165; 11.1.1.1.3, p157; SHP620-303 Resistance Report, Table 10, p41, Section 6.2.2.4, p48.

CI = confidence interval; CMV = cytomegalovirus; HSCT = haemopoietic stem cell transplant; IAT = investigator assigned treatment; HR = hazard ratio; NA = not applicable; NR = not reported; RAS = resistance associated amino acid substitution; SOT = solid organ transplant; **bold** indicates statistically significant results.

[a] Adjusted for transplant type (SOT vs HSCT) and baseline CMV load.

[b] The SOLSTICE CSR and the submission use N = 184 and 65, the numbers of patients with CMV clearance at any time up to 20 weeks, for maribavir and IAT respectively, as the denominator for both recurrence before 8 weeks and recurrence after 8 weeks (SOLSTICE CSR, p172, 179); however, the effect of using the correct denominator for recurrences before 8 weeks is minor.

6.26 A higher proportion of patients randomised to maribavir achieved CMV clearance at 8 weeks, and at any time within the 8-week treatment period. The difference between maribavir and IAT lower in patients infected with CMV without resistance at baseline. Overall, the sensitivity of baseline resistance as a predictor of therapeutic failure among patients allocated to IAT was 80%, and the specificity was 68%. However, the ESC noted that information regarding resistance is unlikely to be available to inform treatment choices in clinical practice.

6.27 The proportion of patients achieving CMV viraemia clearance at week 8 was 15/56 (26.8%) patients treated with ganciclovir/valganciclovir and 9/47 (19.1%) of patients treated with foscarnet (SOLSTICE CSR, p156). Notably, none of the patients given foscarnet were infected with CMV known to be resistant to foscarnet, while 57% of patients given ganciclovir/valganciclovir were infected with CMV known to be resistant to ganciclovir.

6.28 Maribavir may have been less effective in patients with higher viral load. Among maribavir-treated patients, CMV viraemia clearance was achieved at 8 weeks in 36/82

(43.9%) of subjects with high or intermediate viral load (≥ 9100 IU/mL), and in 95/153 (62.1%) of those with low viral load (< 9100 IU/mL). A much smaller difference was seen among IAT-treated patients, of whom 7/32 (21.9%) with high or intermediate viral loads and 21/85 (24.7%) with low viral loads achieved clearance (SOLSTICE CSR, p157).

6.29 Clinical response, defined as improvement or resolution of symptoms of CMV disease present at baseline, may have been more frequent in maribavir-treated patients, but a majority of patients in both treatment groups responded, and the difference in favour of maribavir was smaller than that for virological response. There was no difference between treatment groups in the number of patients developing new symptomatic CMV disease.

6.30 Maribavir resistance developed during treatment in 42 maribavir-treated patients (17.9% of all patients, or 19.6% of those with both baseline and on-treatment viral genotyping). This was associated with treatment failure: 41/42 did not have clearance of CMV viraemia at 8 weeks, and these 41 patients were 39.4% of the 104 maribavir-treated patients who had CMV viraemia at 8 weeks. The evaluation and the ESC considered that if the same rate of development of resistance were to be seen during longer treatment durations efficacy would rapidly be lost. The PSCR stated that one of the key benefits of maribavir is that it can successfully clear CMV viraemia in patients who have failed conventional therapy (including those with resistance). The ESC noted that there was clearance of CMV viraemia in 55.7% of patients treated with maribavir compared to 23.9% of patients taking standard of care, at week 8, suggesting that there was a higher clearance rate associated with maribavir, for the population included in SOLSTICE.

6.31 In terms of quality-of-life outcomes, there were minimal changes in both EQ-5D-5L Index Utility scores and SF-36 during the treatment and follow-up periods, and no meaningful differences between the treatment groups (SOLSTICE CSR pp183-189). Given that most patients had asymptomatic CMV infection, and that CMV infection was, therefore, only a minor component of a complex and difficult illness, this was not surprising.

6.32 Outcomes for patients who received foscarnet as IAT are shown in Table 9. No statistical analysis is presented because this was not a pre-specified comparison.

**Table 9: Outcomes for patients who received foscarnet as IAT**

| | **Maribavir N = 235** | **Foscarnet N = 47** |
|---|---|---|
| CMV viraemia clearance at 8 wk, n (%) | 131 (55.7%) | 9 (19.1%) |
| CMV viraemia clearance and symptom resolution at 8 wk and 16 wk, n (%) | 44 (18.7%) | 4 (8.5%) |
| TEAE, n (%) | 228 (97.4%) | 43 (91.5%) |
| TESAE, n(%) | 90 (38.5%) | 20 (42.6%) |
| TEAE leading to discontinuation of study treatment, n (%) | 31 (13.2%) | 17 (36.2%) |
| Death related to TEAE, n (%) | 16 (6.8%) | 4 (8.5%) |

Source: SOLSTICE CSR, p156; p166; Table 38, p217.
CMV = cytomegalovirus; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent severe adverse event.

6.33 The PSCR provided a post-hoc responder analysis of the primary outcome by IAT treatment. Noting that while this was not pre-specified, the PSCR noted that it showed maribavir has a similar comparative response rate (adjusted difference in proportion responding) versus valganciclovir/ganciclovir (31.7% [18.6-44.8]) and foscarnet (36.4% [23.37-49.4]), compared with the primary comparison as a whole (32.8 % [22.8-42.7]). The pattern observed in the pre-specified analyses, of higher rates of CMV viraemia clearance and of viraemia clearance and symptom control in maribavir-treated patients, appeared to be repeated when the maribavir-treated group was compared with foscarnet-treated patients. There was probably a higher rate of treatment discontinuation among foscarnet-treated patients.

6.34 The ESC noted that subgroup analyses in the CSR (p156) indicated that maribavir was more effective than IAT at clearing CMV viraemia regardless of transplant type. The number (%) of subjects who achieved confirmed CMV viraemia clearance at Week 8 by transplant type was 79/142 (55.6%) for SOT and 52/93 (55.9%) for HSCT in the maribavir group and 18/69 (26.1%) for SOT and 10/48 (20.8%) for HSCT in the IAT group.

**Additional Trials**

6.35 Key results of the trials excluded by the submission but considered relevant are shown in Table 10.

6.36 The most notable differences between these trials and SOLSTICE are the exclusion of patients infected with CMV with mutations conferring resistance to ganciclovir, and the requirement in NCT02927067 that patients were experiencing their first post-transplant CMV infection and had no CMV organ disease. These exclusion criteria did not make the population in NCT02927067 dissimilar to that in SOLSTICE, in which 68.2% of patients were experiencing their first post-transplant CMV infection and there were few patients with CMV organ disease (SOLSTICE CSR, Table 16, p136, and Table 7). The ESC also noted that in NCT02927067 only patients with HSCT were included (not SOT).

**Table 10: Results of relevant but excluded trials**

| **NCT02927067**<br>**N = 553** | | | |
|---|---|---|---|
| | **Maribavir**<br>**N = 276** | **Valganciclovir**<br>**N = 277** | **Adjusted difference (95% CI)**<br>**maribavir – valganciclovir**[a] |
| Completed 8 week treatment, n (%) | 179 (64.9%) | 140 (50.5%) | NR |
| CMV viraemia clearance at 8 week, n (%) | 190 (68.8%) | 212 (76.5%) | **- 7.7% (-15.0, -0.36)**[c] |
| New resistance to ganciclovir or foscarnet or cidofovir or maribavir[b], n (%) | 24 (8.8%) | 8 (2.9%) | NR |
| All-cause mortality, n (%) | 37 (13.4%) | 29 (10.5%) | NR |
| **Maertens et al, 2019**<br>**N = 161** | | | |
| | **Maribavir 400 mg bd**<br>**N = 39** | **Valganciclovir**<br>**N = 40** | **Risk ratio (95% CI)**<br>**maribavir/valganciclovir** |
| CMV viraemia clearance within 3 week, n (%) | 26 (66.7%) | 22 (55.0%) | 1.18 (0.86, 1.63) |
| CMV viraemia clearance within 6 week, n (%) | 31 (79%) | 26 (67%) | 1.19 (0.92, 1.55) |
| Death, n (%) | 2 (5%) | 3 (8%) | NR |

Source: https://clinicaltrials.gov/study/NCT02927067 (accessed 15 July, 2023); Maertens J, Cordonnier C, Jaksch P, Poire X et al. Maribavir for pre-emptive treatment of cytomegalovirus reactivation. NEJM 2019; 381(12):1136-1147.

bd = twice daily; CI = confidence interval; CMV = cytomegalovirus; NR = not reported

[a] Adjusted for baseline plasma CMV DNA concentration and acute GVHD status.

[b] Up to 20 week from start of treatment.

[c] The trial was designed to test for non-inferiority, with a non-inferiority margin of -7%. The hypothesis of non-inferiority was therefore rejected.

6.37 Taking the trials together, and considering that NCT02927067 is much larger, and double-blind, the evidence suggests that maribavir may be inferior to valganciclovir in infections not resistant to ganciclovir. This supports the observation in SOLSTICE of a much smaller difference between the response proportions for maribavir and IAT in patients whose infection was refractory to current treatment but not resistant, than in those whose infection was refractory and resistant.

6.38 NCT02927067 observed a higher rate of development of resistance mutations in patients treated with maribavir than in those treated with valganciclovir, as also seen in SOLSTICE.

6.39 The ESC considered that while the results of the excluded trials could not be ignored, patients in the SOLSTICE trial were more reflective of the requested patient population, noting that determination of genotypic resistance is not clinical practice in Australia.

## *Comparative harms*

6.40 Key adverse events in SOLSTICE are shown in Table 11.

**Table 11: Summary of key adverse events in the SOLSTICE trial**

| | Maribavir N = 235 | IAT N = 117 |
|---|---|---|
| Deaths at any time[a] | 27 (11.5%) | 13 (11.2%) |
| Deaths during 8 week treatment phase | 14 (6.0%) | 5 (4.3%) |
| Deaths attributed to CMV | 4 (1.7%) | 3 (2.6%) |
| TEAE, n (%) | 228 (97.4%) | 106 (91.4%) |
| TESAE, n (%) | 90 (38.5%) | 43 (37.1%) |
| Severe TEAE, n (%) | 75 (32.1%) | 44 (37.9%) |
| TEAE or TESAE leading to discontinuation of study treatment, n (%) | 51 (21.7%) | 54 (46.2%) |
| Infections reported as SAE, n (%) | 53 (22.6%) | 17 (14.7%) |
| Infections leading to discontinuation of study treatment, n (%) | 17 (7.3%) | 8 (6.9%) |
| Disturbance of taste, n (%) | 87 (37.2%) | 4 (3.4%) |
| Disturbance of taste leading to discontinuation of study treatment, n (%) | 2 (0.9%) | 0 |
| Neutropenia, n (%) | 22 (9.4%) | 26 (22.4%) |
| Neutropenia leading to discontinuation of study treatment, n (%) | 0 | 11 (9.5%) |
| Febrile neutropenia, n (%) | 2 (0.9%) | 4 (3.4%) |
| Increased serum creatinine, n (%) | 13 (5.6%) | 5 (4.3%) |
| Acute kidney injury, n (%) | 4 (1.7%) | 9 (7.8%) |
| RAS developing during study conferring resistance to ganciclovir, foscarnet or cidofovir, n/N[b] (%) | 28/217 (12.9%) | 5/103 (4.9%) |
| RAS developing during study conferring resistance to maribavir, n/N[b] (%) | 42/217 (19.6%) | 0 |

Source: SOLSTICE CSR: Table 40, p224; Table 41, p227; Table 42, pp229-230; p231; Submission: Table 2.5.5, p79, Table 2.5.11, p85, Table 2.5.12, pp87-88, Table 2.5.15, pp90-91.

CMV = cytomegalovirus; IAT = investigator assigned treatment; RAS = resistance-associated amino acid substitution; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

[a] Including two deaths in each group occurring after completion of 20-week treatment + follow-up period but due to events beginning before 20 weeks.

[b] N = number of patients with baseline and post-baseline viral genotype.

6.41 The overall rates of most adverse events, and the numbers of deaths, were similar in maribavir and IAT groups. Serious adverse events (SAEs) of infection may have been more common in maribavir-treated patients; the SOLSTICE CSR attributes this to "longer exposure to maribavir, which allowed more time for infections to develop in this immunocompromised population" (SOLSTICE CSR, p18). Disturbance of taste ("dysgeusia") was common in patients treated with maribavir, as previously reported, but rarely required discontinuation of treatment. Neutropenia was less common in maribavir-treated patients, also as previously reported, and was a common cause of treatment discontinuation in IAT-treated patients.

6.42 New resistance mutations to maribavir were common (19.6%) in CMV from maribavir-treated patients, but were not seen in IAT treated patients. New mutations conferring resistance to ganciclovir, foscarnet or cidofovir were also more common in maribavir-treated patients (12.9%) than in IAT-treated patients (4.9%). There were 28 mutations identified; most (19/28) were in the UL97 gene, and conferred resistance to maribavir and ganciclovir (16/19), or to ganciclovir alone (3/19). However, 9/28 were in UL54; 5/9 conferred resistance to ganciclovir and cidofovir, 2/9 conferred resistance to foscarnet, and 2/9 to all three drugs. None of the patients whose CMV developed resistance to cidofovir while they were receiving maribavir had received cidofovir previously, and only one of the patients whose CMV developed foscarnet resistance

while they were receiving maribavir had received foscarnet previously (SHP620-303 Resistance Report, Table 13, p44). The Pre-PBAC response noted that replication of CMV in the presence of antiviral therapy, subtherapeutic dosing and limited host immunity are known risk factors for the development of antiviral drug resistance in post-transplant CMV. The longer average time on treatment for maribavir (mean exposure 52.5 vs 36.0 days) likely contributed to a higher rate of resistance detection when compared to the IAT. The Pre-PBAC response also note that 58% (30/52) of patients with emergent maribavir drug related mutations reported viraemia clearance with alternative treatments.

## *Benefits/harms*

6.43 A benefits/harms summary is not presented as the comparison of maribavir with all four drugs included in the IAT arm of SOLSTICE was not clinically reasonable as they have different efficacy and safety profiles.

## *Clinical claim*

6.44 The submission described maribavir as superior in terms of effectiveness compared to standard medical management. The ESC considered the clinical claim was highly uncertain. The ESC considered that while maribavir is likely to be more efficacious than standard of care in patients representative of those treated in the SOLSTICE trial, the development of resistance to maribavir is a significant issue, and based on the excluded NCT0297067 trial, efficacy in patients undergoing HSCT was uncertain. The ESC also considered that a key issue was the high risk of bias in the open label SOLSTICE trial, resulting in a likely overestimate of benefit for maribavir.

6.45 The submission described maribavir as superior in terms of safety compared to standard medical management. This claim was not adequately supported. The adverse events in SOLSTICE and NCT02927067 showed a lower rate of neutropenia, and suggest a lower incidence of febrile neutropenia, with maribavir compared to ganciclovir/valganciclovir, but the rate of febrile neutropenia was low and there was no evidence that maribavir was superior in this regard to foscarnet. There may have been a higher rate of acute kidney injury in IAT-treated patients, but cases were few, and confined to foscarnet-treated patients. The ESC considered that the development of resistance to maribavir was an additional concern.

6.46 The PBAC considered that the claim of superior comparative effectiveness was not well-supported by the data.

6.47 The PBAC considered that the claim of superior comparative safety was not adequately supported by the data.

## *Economic analysis*

6.48 The submission presented a stepped economic evaluation, based on SOLSTICE and retrospective studies of SOT and HSCT patients (TAK620-5001 and TAK620-5002; referred to as OTUS = Outcomes, Treatment Patterns and Healthcare Resource

Utilization Study). Clinicaltrials.gov does not list these two studies, which took place in Europe and the US but does list two corresponding retrospective OTUS studies which are currently recruiting, and are located in Europe and Canada.

6.49 The OTUS studies were retrospective reviews of medical records and therefore the results are subject to a high level of bias.

6.50 The economic evaluation presented was a cost-utility analysis. The ESC noted that efficacy may have been short-lived in some patients (where resistance developed).

6.51 The evaluation considered there were three main areas contributing to unreliability for the economic model presented by the submission:

1) Clinical data: The cost-utility analysis presented by the submission was not adequately supported by the clinical evidence. The ESC considered the claim of superior effectiveness was highly uncertain. Also, the clinical data were not applied in a reasonable manner, as there was no evidence to support the use of week 8 clearance or mortality data out to 78 weeks in Stage 1 of the model; and the evidence used to support the 78 week duration of Stage 1 was based on small numbers of patients (further discussion of the 78 week duration of Stage 1 is at paragraphs 6.54 to 6.56).
2) Model results were highly variable: Sensitivity analyses presented by the submission showed considerable variability in model results, from a decrease of 93.6% to an increase of 300.6%, or dominance by maribavir. As the model results were based on inadequate clinical data and poorly justified assumptions they were considered by the evaluation and the ESC to be of limited value.
3) The presentation of the model was unnecessarily complex as the model included over 3,400 variable names. While not all names were active in the Australian version of the model, the use of multiple names for the same variables, made tracing events and costs difficult.

6.52 The ESC agreed with the evaluation that the model is not likely to be reliable for decision-making, as it was informed by selective data sources and unjustified assumptions, that all favoured maribavir.

**Table 12: Summary of model structure, key inputs and rationale**

| Component | Summary |
|---|---|
| Treatments | Maribavir vs IAT (ganciclovir, valganciclovir, foscarnet, cidofovir) |
| Time horizon | 10 years in the model base case versus 20 weeks in SOLSTICE |
| Outcomes | QALYs and life years |
| Methods used to generate results | Markov model |
| Health states | The model was separated into two stages: 1) 0 – 78 weeks and 2) 78 weeks to end of the time horizon.<br>Stage 1: Onset of R/R CMV and includes a three state Markov model with the states:<br>i) csCMV, ii) n-csCMV and iii) dead.<br>Stage 2: Two state Markov model with the states: i) alive or ii) dead. |
| csCMV | All patients enter the model with clinically significant R/R CMV requiring treatment. This state is occupied by patients who do not achieve CMV viraemia clearance (i.e., clearance defined as plasma CMV DNA concentration <LLOQ) or patients who in a previous cycle occupied the n-csCMV health state but then experience a clinically significant recurrence (i.e., plasma CMV DNA concentration >LLOQ which requires treatment). |
| n-csCMV | Defined as patients who have plasma CMV DNA <LLOQ or CMV DNA >LLOQ not requiring treatment. Subjects who achieve CMV clearance or subjects who have achieved clearance and do not experience a clinically significant recurrence occupy the n-csCMV health state. |
| Cycle length | 4 weeks for 3 years then annual cycles |
| Transition probabilities | Based on clearance, recurrence, and mortality:<br>Clearance: SOLSTICE CSR<br>Recurrence (clinically significant): SOLSTICE and OTUS<br>Mortality: Week 0 to 8 – SOLSTICE IPD analysis;<br>Week 8 to end Stage 1 – SOLSTICE IPD analysis;<br>Stage 2 (Week 78 onwards) – literature based, specific to SOT (NHS Organ Donation and Transplantation Annual activity report) and HSCT (Haematological Malignancy Research Network/Martin 2010). |
| Extrapolation method | Clearance and recurrence were not extrapolated. Mortality in Stage 2 of the model (week 78 onward) was literature based and for HSCT mortality beyond 5 years data from Martin 2010 was used and extrapolated. No other mortality data was extrapolated. |
| Health related quality of life | EQ-5D data from SOLSTICE; also a TTO study. |

| Health state | Maribavir and IAT | Source |
|---|---|---|
| **SOT** | | |
| n-csCMV | 0.838 | Solstice IPD analysis |
| csCMV | 0.639 | Solstice IPD analysis + TTO |
| **HSCT** | | |
| n-csCMV | 0.694 | Solstice IPD analysis |
| csCMV | 0.502 | Solstice IPD analysis + TTO |

Source: Table 3.1.1, p112, Table 3.5.3, p140; Section 3.2.2.1, p119-120 of the submission.
csCMV = clinically significant cytomegalovirus; HSCT = haematopoietic stem cell transplant; HSCT = haemopoietic stem cell transplant; IAT = investigator assigned treatment; IPD = individual patient data; LLOQ = lower limit of quantification; n-csCMV = non-clinically significant cytomegalovirus; R/R = resistant, refractory; SOT = solid organ transplant; TTO = time trade off

6.53 The model submitted was very similar to those considered by NICE in 2022 and 2023. The model assessed by NICE in 2022 was also a two-stage Markov model, although the first stage went from 0 to 52 weeks, instead of 78 weeks as in the submission's model. NICE considered that the model assessed in 2022 was not fit for purpose. Following assessment by NICE, Stage 1 in the 2022 model was lengthened to 78 weeks, and then for the 2023 model, Stage 1 was shortened to 39.2 weeks.

6.54 The key difference between the model accepted by NICE and the current model is the submission's maintenance of the 78-week duration of Stage 1 of the model. The submission justified use of a 78-week duration for Stage 1 on the basis of OTUS data. The submission stated data from OTUS indicate patients may experience multiple recurrences, and under the assumption that treatment occurs for 35.98 days (average time on treatment in the IAT arm in SOLSTICE) and the time between each recurrent episode reflects the duration of clearance, it can be inferred from the OTUS data that CMV events can recur after 155.4 weeks from the start of the index episode for SOT patients and after 77.1 weeks from the start of the index episode for HSCT patients. The submission added that while the data from OTUS provide evidence the Stage 1 Markov model could exceed 78 weeks (i.e., 155.4 weeks for SOT), clinicians indicated treatment patterns for patients can be highly heterogenous and would be determined on a case-by-case basis. The submission therefore assumed that transitioning to the Stage 2 model at 78 weeks was considered a pragmatic assumption. The OTUS data for recurrence provided by the submission is provided in Table 13.

**Table 13: Data from OTUS used to determine Stage 1 duration**

| CMV episode | Recurrence (patient numbers) | Days to start of new episode | Treatment duration (days) | Cumulative duration since index episode | |
|---|---|---|---|---|---|
| | | | | Days | Weeks |
| **SOT** | | | | | |
| 1 (CMV index episode) | - | 0 | 35.98 | 35.98 | 5.14 |
| 2 | 1 (N=47) | 117.51 | | 189.47 | 27.07 |
| 3 | 2 (N=10) | 99.70 | | 325.15 | 46.45 |
| 4 | 3 (N=4) | 653.50 | | 1014.63 | 144.95 |
| 5 | 4 (N=1) | 37 | | 1087.61 | 155.37 |
| **HSCT** | | | | | |
| 1 (CMV index episode) | - | 0 | 35.98 | 35.98 | 5.14 |
| 2 | 1 (N=88) | 47.41 | | 119.37 | 17.05 |
| 3 | 2 (N=34) | 45.06 | | 200.41 | 28.63 |
| 4 | 3 (N=15) | 21.73 | | 258.12 | 36.87 |
| 5 | 4 (N=10) | 32.40 | | 326.50 | 46.64 |
| 6 | 5 (N=4) | 130 | | 492.48 | 70.35 |
| 7 | 6 (N=2) | 47.50 | | 575.96 | 82.28 |

Source: Table 3.2.2, p117; Table 3.2.3, p118 of the submission.
CMV = cytomegalovirus; HSCT = haematopoietic stem cell transplant; SOT = solid organ transplant

6.55 The PSCR confirmed that the time period used was the duration from the start of the CMV index episode to the start of the sixth recurrence, excluding the treatment period (35.98 days or 5.14 weeks) of the sixth recurrence. Therefore, for HSCT, 82.28 weeks – 5.14 weeks = 77.1 weeks. For SOT, the duration was 150.2 weeks (155.37 weeks – 5.14 weeks = 150.2 weeks). The PSCR stated that given OTUS represents the best available data source on CMV recurrence, it would be reasonable to use this data source as the basis of Stage 1 length. One of the key changes made to the model accepted by NICE in 2023 was the shortening of Stage 1 to 39.2 weeks from 78 weeks. A duration of 39.2 weeks was accepted by NICE because this was the time frame over which the first and second recurrences happened in OTUS and the data for this was

more robust. The ESC noted that the recurrence data used from OTUS was based on very small patient numbers, especially for third and later recurrences. The ESC considered that given the small number of patients in the OTUS data it was not a reliable basis for informing the Stage 1 model length. When Stage 1 in the submission's model was shortened to 39.2 weeks, the ICER increased by 128% to $115,000 to < $135,000/QALY (see Table 16).

6.56 The evaluation and the ESC considered that assuming the IAT treatment duration from SOLSTICE of 35.98 days would apply across all recurrences is not likely to represent actual treatment duration as treatment duration may vary across recurrences.

6.57 Table 14 lists the key issues with the model, with further description in the paragraphs following the table.

**Table 14: Key issues with the model**

| Component | Description | Impact<br>Base case: [1]/QALY gained |
|---|---|---|
| Stage length | Stage 1 length of 78 weeks was based on recurrences in OTUS, but this data was based on small patient numbers (1 for SOT; 2 for HSCT) and assumed treatment duration of 35.98 days for all recurrences, when treatment duration for recurrences is likely to vary. | High, favours maribavir<br>Shortening the stage length to 52 weeks increased the ICER to [2]/QALY gained and shortening it to 39.2 weeks (as accepted by NICE) increased the ICER to [4]/QALY. |
| Clinical data | Clearance and mortality data from SOLSTICE at 8 weeks were assumed to apply for 78 weeks. | There was no evidence to support this, and the impact could not be assessed. |
| Comparator drug prices | Foscarnet and cidofovir prices selected were not adequately justified. | High, favours maribavir<br>If price is dropped by 50% the ICER increased to [3]. |
| Model duration | The submission's selection of the 10-year time horizon was not adequately justified, particularly given no CMV events were assumed to occur following 78 weeks or 1.5 years. | High, favours maribavir<br>Shortening the model to 5 years increased the ICER to [2] and shortening it to 2 years increased the ICER to [4]/QALY gained. |

Source: compiled during the evaluation.
CMV = cytomegalovirus; HSCT = haematopoietic stem cell transplant
*The redacted values correspond to the following ranges:*
[1] *$45,000 to < $55,000*
[2] *$75,000 to < $95,000*
[3] *$95,000 to < $115,000*
[4] *$115,000 to < $135,000*

6.58 Application of the clinical data in the model is provided below:

- Clearance: the first health state transition events in the model occur at week 8 and are based on the primary endpoint value from SOLSTICE (confirmed CMV viraemia clearance at the end of Week 8). These values were used directly to inform the transition between the csCMV and n-csCMV health state between weeks 0 to 8. Clearance probabilities from week 8 to week 78 were derived from the week 8 response for the IAT arm of SOLSTICE, as patients can only receive IAT treatment from week 8 onward. The submission provided no justification or evidence supporting the use of week 8 clearance data for 78 weeks.
- Recurrence: rates of recurrence between week 8 and week 20 were treatment-specific and were sourced from SOLSTICE. This differed from the model accepted

by NICE, where recurrence was assumed to be treatment independent for the model duration. Recurrence from week 21 onward was sourced from OTUS and was considered independent of treatment. The ESC considered that the submission did not adequately justify the use of treatment-specific recurrence from SOLSTICE followed by treatment-independent recurrence from OTUS.

- Mortality: transition probabilities for mortality from week 8 to week 78 were based on SOLSTICE and were classified according to response (patients achieving clearance) and no response (patients not achieving clearance) at week 8 for each transplant type. The submission provided no justification for applying data from week 8 to week 20 in SOLSTICE up to 78 weeks. Mortality from week 78 onward was based on transplant type, using various literature-based data.

The ESC considered that the selective application of the different data sources to the various transition probabilities and stages of the model was poorly justified and added substantial uncertainty to the modelled outcomes.

6.59 The utility values applied in the model were sourced from EQ-5D-5L data collected in SOLSTICE and results from a time-trade-off (TTO) study conducted in the UK. The EQ-5D-5L responses were mapped to EQ-5D-3L responses by a crosswalk algorithm using Van Hout 2012, following NICE guidelines. The submission provided no explanation as to why Australian mapping was not used. The submission reported there was no significant effect based on treatment, but there was a statistically significant effect based on response and transplant type. Thus, the utility values applied in the model were the same for both treatment arms, and were different for SOT and HSCT patients. The TTO study included 1,020 participants from the general public who responded to a series of vignettes. It was unknown how many respondents contributed to each health state/response type used in the TTO study.

6.60 The model duration of 10 years was not adequately justified by the submission, which, citing the July 2018 and March 2019 letermovir submissions, claimed that the PBAC considered 10 years to be an appropriate time horizon in the economic evaluation of CMV treatments. The PBAC did not comment directly on the model duration for letermovir, and while ESC in July 2018 indicated that a 10-year time horizon may be reasonable to capture the life years gained from deaths avoided due to CMV infections, there were other issues that rendered the letermovir model unreliable. The PSCR stated the 10-year time horizon assumption should be considered conservative in the context of other Health Technology Assessment agencies where lifetime time horizons (47 years) have been accepted for economic evaluations for maribavir in this patient population. The ESC considered that that the submission's selection of a 10-year time horizon was not adequately justified, particularly given no CMV events were assumed to occur after 78 weeks.

6.61 The model used a 4-week cycle for 3 years and then annual cycles for the remainder of the 10 years. The reason for this change in cycle duration was not discussed by the

submission. The 2022 NICE document[5] reported this was done to allow the model to be flexible and to have the ability to include further CMV occurrences beyond 12 months. The impact on model results of a change in cycle length could not be assessed without considerable changes to the model, so the role of the submission's selected change in cycle length is unknown.

6.62 The ESC noted that the model relied on assumed prices for foscarnet and cidofovir, and that varying these prices had a substantial impact on the ICER. While the submission justified the prices used for foscarnet and cidofovir on the basis that the drugs are currently funded through state-level tenders or hospital purchase, the submission did not provide any justification for the actual values applied. The PSCR stated that prices for these therapies were based on sponsor estimates as the sponsor does not have visibility of the individual hospital formulary and state-level tenders. The ESC considered that this emphasises the usefulness of the sensitivity analysis that showed a potential 94% increase in the ICER when the price of these therapies was reduced by 50%.

6.63 The PSCR stated that the submission used PBS pricing for valganciclovir and ganciclovir as a proxy. The ESC considered this was reasonable given these therapies are likely being used off-label for the requested patient population on the PBS.

6.64 Overall, the model had structural issues (model duration not adequately justified; Stage 1 length not supported) and input issues (assumed response at 8 weeks will be maintained for 78 weeks without evidence for such; applied comparator drug costs that have not been justified) that render the model results unreliable.

6.65 The model results are provided in Table 15.

[5] https://www.nice.org.uk/guidance/ta860/documents/committee-papers

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

| Step and component | Maribavir | IAT | Increment |
|---|---|---|---|
| **Step 1: Trial-based costs and outcomes at 8 weeks** | | | |
| Costs | [redacted] | $17,609 | [redacted] |
| Responder (clearance) | 55.70% | 23.90% | 31.80% |
| Incremental cost/responder | | | [redacted][2] |
| **Step 2: Time horizon extended to 78 weeks** | | | |
| Costs | [redacted] | $81,897 | [redacted] |
| LY | 1.18 | 1.16 | 0.02 |
| Incremental cost/extra LY gained | | | [redacted][3] |
| **Step 3: Time horizon extended to 10 years** | | | |
| Costs | [redacted] | $82,886 | [redacted] |
| LY | 4.69 | 4.56 | 0.13 |
| Incremental cost/extra LY gained | | | [redacted][2] |
| **Step 4: Utility weights applied** | | | |
| Costs | [redacted] | $82,886 | [redacted] |
| QALYs | 3.52 | 3.39 | 0.13 |
| **Incremental cost/extra QALY gained (base case)** | | | [redacted][1] |

Source: Table 3.8.1, p151 of the submission.
IAT = investigator assigned treatment; LY = life year; QALY = quality adjusted life year
*The redacted values correspond to the following ranges:*
[1] *$45,000 to < $55,000*
[2] *$55,000 to < $75,000*
[3] *$255,000 to < $355,000*

6.66 Sensitivity analyses showed the model results were highly variable. A summary of key sensitivity analyses is provided in Table 16.

**Table 16: Results of sensitivity analyses – economic model**

| Analyses | Incremental cost ($) | Incremental QALY | ICER | % change ICER |
|---|---|---|---|---|
| **Base case** | [redacted] | **0.13** | [redacted][1] | **-** |
| Time horizon (base case: 10 years) | | | | |
| 12 years | [redacted] | 0.15 | [redacted][1] | - [redacted]% |
| 5 years | [redacted] | 0.09 | [redacted][2] | + [redacted]% |
| 2 years | [redacted] | 0.06 | [redacted][3] | + [redacted]% |
| Discount rate (base case: 5%) | | | | |
| 3.5% | [redacted] | 0.14 | [redacted][1] | - [redacted]% |
| 0% | [redacted] | 0.16 | [redacted][4] | - [redacted]% |
| Comparator – proportion treated with each drug (base case: valganciclovir 25.4%, ganciclovir 25.9%, foscarnet 43.5%, cidofovir 5.2%) | | | | |
| 25% with each drug | [redacted] | 0.13 | [redacted][2] | + [redacted]% |
| 100% with ganciclovir | [redacted] | 0.13 | [redacted][3] | + [redacted]% |
| 100% with valganciclovir | [redacted] | 0.13 | [redacted][5] | + [redacted]% |
| 100% with cidofovir | [redacted] | 0.13 | [redacted][3] | + [redacted]% |
| 100% with foscarnet | [redacted] | 0.13 | dominant | |
| 50% foscarnet/ 50% cidofovir | [redacted] | 0.13 | [redacted][6] | - [redacted]% |
| 50% valganciclovir/ 50% ganciclovir | [redacted] | 0.13 | [redacted][7] | + [redacted]% |
| Maribavir mean time on treatment (base case: 7.5 weeks) | | | | |
| 4 weeks | - [redacted] | 0.13 | dominant | |
| 8 weeks | [redacted] | 0.13 | [redacted][8] | + [redacted]% |
| Re-treatment (base case: with IAT) | | | | |
| With maribavir | [redacted] | 0.28 | dominant | |
| Risk of CMV-related mortality from week 8 onward for SOT and HSCT (base case: SOLSTICE) | | | | |
| Literature based | [redacted] | 0.05 | [redacted][2] | + [redacted]% |
| Mortality from week 78 onward (base case: literature-based) | | | | |
| SOLSTICE-based | [redacted] | 0.13 | [redacted][1] | + [redacted]% |
| Utility values (base case: SOLSTICE and TTO) | | | | |
| Literature based | [redacted] | 0.13 | [redacted][1] | + [redacted]% |
| SOLSTICE imputation values only | [redacted] | 0.12 | [redacted][8] | + [redacted]% |
| Stage 1 duration (base case: 78 weeks) | | | | |
| 39.2 weeks (accepted by NICE) | [redacted] | 0.10 | [redacted][3] | + [redacted]% |
| 52 weeks | [redacted] | 0.11 | [redacted][2] | + [redacted]% |
| 82 weeks | [redacted] | 0.14 | [redacted][1] | - [redacted]% |
| Adverse events (base case: cost and disutilities included) | | | | |
| Remove cost for dysgeusia | [redacted] | 0.13 | [redacted][1] | - [redacted]% |
| Exclude AEs (cost and disutilities) | [redacted] | 0.13 | [redacted][2] | + [redacted]% |
| Cost of foscarnet and cidofovir (base case: foscarnet $2,000 DPMQ; cidofovir $1,100 DPMQ) | | | | |
| $1,000 foscarnet/$550 cidofovir (-50%) | [redacted] | 0.13 | [redacted][9] | + [redacted]% |
| $1,500 foscarnet/$825 cidofovir (-25%) | [redacted] | 0.13 | [redacted][2] | + [redacted]% |

Source: Table 3.9.1, p154 of the submission.

AE = adverse event; GVHD = graft versus host disease; HSCT = haematopoietic stem cell transplant; SOT = solid organ transplant; TTO = time trade off

*The redacted values correspond to the following ranges:*

[1] *$45,000 to < $55,000*

[2] *$75,000 to < $95,000*

[3] *$115,000 to < $135,000*

[4] *$35,000 to < $45,000*

[5] *$155,000 to < $255,000*

[6] *$15,000 to < $25,000*

[7] *$135,000 to < $155,000*

[8] *$55,000 to < $75,000*

[9] *$95,000 to < $115,000*

6.67 Altering the duration of Stage 1 of the model had considerable impact on the ICER/QALY. When Stage 1 was shortened to 39.2 weeks, the ICER/QALY increased to $115,000 to < $135,000, an increase of almost 130%. When Stage 1 was shortened to 52 weeks, the ICER increased to $75,000 to < $95,000/QALY. The ESC considered that the shorter Stage 1 length of 39.2 weeks would be appropriate to reduce uncertainty in the model.

6.68 The ESC noted that the model was also sensitive to overall duration, as decreasing the model duration to 5 years increased the ICER/QALY by over 40% to $75,000 to < $95,000 and decreasing it to 2 years increased the ICER to $115,000 to < $135,000, an increase of over 125%.

6.69 The ICER/QALY varied considerably when the proportion treated with each IAT drug was changed. In the base case the submission assumed that 25% would be treated with valganciclovir, 25% treated with ganciclovir, 44% treated with foscarnet and 5% treated with cidofovir. When the proportions were changed to 25% treated with each drug, the ICER/QALY increased by 66% to $75,000 to < $95,000. If all IAT patients were treated with valganciclovir, the ICER increased to $155,000 to < $255,000, whereas if all IAT patients were treated with foscarnet, maribavir became dominant (although this result was dependent on the price assumed for foscarnet, which may not be accurate and has not been established as cost-effective by the PBAC). The ESC noted that the split of IAT treatments for this population in Australian clinical practice is unknown.

6.70 The ESC noted that the model also relied on assumed prices for foscarnet and cidofovir, and that varying these prices had a substantial impact on the ICER.

6.71 The evaluation and the ESC considered that the considerable variability in model results demonstrate that the model is not reliable for decision-making.

6.72 Overall, the ESC considered the model contained many unsupported assumptions, as well as unjustified and selective use of data, which made it very difficult to interpret the direction and the magnitude of uncertainty. For decision-making purposes, the ESC considered that considerably better justification of inputs to the model would be required, as well as simplification of the modelling approaches by, for example, removing the dual approach to treatment independent and treatment dependent transition probabilities obtained from different sources. The ESC considered that the cost of maribavir should reflect the uncertainty in the clinical data and the short duration of efficacy in patients who develop resistance.

### *Drug cost/patient/course*

6.73 The submission provided the intervention cost (undiscounted) per patient over the 10-year model duration. The submission indicated this cost was $[redacted] for maribavir. This represented the cost for first treatment, which would have a duration of 7.5 weeks based on the mean treatment duration in SOLSTICE. For IAT, treatment duration was

5.14 weeks. The submission stated that clinical experts have noted that patients receive a single dosing regimen until the CMV has cleared.

**Table 17: Drug cost per patient for maribavir and IAT**

| | Maribavir | | | IAT | | |
|---|---|---|---|---|---|---|
| | Trial dose and duration | Model | Financial estimates | Trial dose and duration | Model | Financial estimates |
| Mean dose | 400 mg/bid | 400 mg/bid | 400 mg/bid | Varies[a] | Varies[a] | Model cost applied |
| Mean duration | 7.5 weeks | 7.5 weeks | 7.5 weeks | 5.14 weeks | 5.14 weeks | |
| Cost/patient/course | - | [redacted] | [redacted] | - | $7,908 | |

Source: Section 3.8.1, p151 of the submission; Excel workbook 'Attachment 3.1 – Maribavir_CEM_FINAL'.
bid = twice daily; IAT = investigator assigned treatment
[a] The dose of the four IAT drugs (ganciclovir, valganciclovir, foscarnet and cidofovir) varied considerably and are not reported in this table.

6.74 The model-based costs in Table 17 are not likely to be accurate, given the identified issues with the model.

## *Estimated PBS usage & financial implications*

6.75 This submission was considered by DUSC. The submission used an epidemiological approach to calculate the financial estimates. The inputs are summarised in Table 18.

**Table 18: Key inputs for financial estimates**

| Component | Data source |
|---|---|
| **Epidemiology** | |
| Eligible patients | Estimates were provided for SOT and HSCT patients.<br>Number with SOT and number with HSCT: For SOT this was based on the Australia and New Zealand Organ Donation Registry (ANZOD) 2022 annual report and the Australia and New Zealand Dialysis & Transplant Registry (ANZDATA) 2013 to 2022 annual reports. From this data the submission calculated an average yearly growth rate of 3.86%.<br>For the HSCT population the submission used the Australia and New Zealand Transplant and Cellular Therapies (ANZTCT) registry annual data summary reports for 2014 to 2021. The submission calculated an average yearly growth rate of 4.38% using 2015 to 2019 data and a second yearly growth rate of 3.61% using 2015 to 2021 data. While the 3.61% growth rate was not mentioned in the submission, it was used in the submission's Section 4 Excel workbook, along with the 4.38% growth rate, to estimate HSCT patient numbers. For both SOT and HSCT, the submission stated 2020 and 2021 data were excluded from the growth rate calculation due to decrease in transplant activity during the COVID-19 pandemic.<br>Proportion with CMV infection: Based on data sourced from 35 publications obtained in a literature search conducted by the submission, the submission calculated a weighted average of 22.8% for SOT and 34.0% for HSCT.<br>Proportion of CMV patients resistant, refractory or intolerant: Literature sources were used to estimate the proportion of patients with resistant, refractory or intolerant CMV infection. For the intolerant population the submission indicated no literature sources were available and therefore assumed similar relative proportions of resistant, refractory and intolerant patients from OTUS and estimated proportions for both the SOT and HSCT populations. The proportions assumed are listed in the table below. |

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|---|---|---|---|---|---|---|
| **SOT** | | | | | | |
| SOT patients | 1,665 | 1,729 | 1,796 | 1,865 | 1,937 | 2,012 |
| Number of SOT patients with CMV infection (22.8%) | 379 | 394 | 409 | 425 | 441 | 458 |
| Resistant (5.3%) | 20 | 21 | 22 | 23 | 23 | 24 |
| Refractory (21.7%) | 82 | 85 | 89 | 92 | 96 | 99 |
| Intolerant (10%) | 38 | 39 | 41 | 42 | 44 | 46 |
| Total eligible SOT | 140 | 146 | 151 | 157 | 163 | 169 |

<table>
<tr><th>Component</th><th>Data source</th></tr>
<tr><td></td><td>
<table>
<tr><td>HSCT</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>HSCT patients</td><td>655</td><td>684</td><td>714</td><td>745</td><td>778</td><td>812</td></tr>
<tr><td>Number of HSCT patients with CMV infection (34.0%)</td><td>223</td><td>232</td><td>243</td><td>253</td><td>264</td><td>276</td></tr>
<tr><td>Resistant (5.2%)</td><td>12</td><td>12</td><td>13</td><td>13</td><td>14</td><td>14</td></tr>
<tr><td>Refractory (32.0%)</td><td>71</td><td>74</td><td>78</td><td>81</td><td>85</td><td>88</td></tr>
<tr><td>Intolerant (20%)</td><td>45</td><td>46</td><td>49</td><td>51</td><td>53</td><td>55</td></tr>
<tr><td>Total eligible HSCT</td><td>127</td><td>133</td><td>139</td><td>145</td><td>151</td><td>158</td></tr>
<tr><td>Totals (SOT + HSCT)</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Transplant patients</td><td>2,320</td><td>2,413</td><td>2,510</td><td>2,610</td><td>2,715</td><td>2,824</td></tr>
<tr><td>CMV infection</td><td>602</td><td>626</td><td>651</td><td>678</td><td>705</td><td>734</td></tr>
<tr><td>Eligible patients – SOT and HSCT</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Resistant</td><td>32</td><td>33</td><td>34</td><td>36</td><td>37</td><td>39</td></tr>
<tr><td>Refractory</td><td>153</td><td>160</td><td>166</td><td>173</td><td>180</td><td>188</td></tr>
<tr><td>Intolerant</td><td>82</td><td>86</td><td>89</td><td>93</td><td>97</td><td>101</td></tr>
<tr><td>Total eligible</td><td>267</td><td>278</td><td>290</td><td>302</td><td>314</td><td>327</td></tr>
</table>
</td></tr>
<tr><td colspan="2">Utilisation</td></tr>
<tr><td>Uptake and treatment</td><td>
Uptake: [redacted]% in Year 1, [redacted]% in Year 2, [redacted]% in Year 3, [redacted]% in Years 4 to 6; sponsor assumption.<br>
Grandfathered patients: None.<br><br>
<table>
<tr><th></th><th>Year 1</th><th>Year 2</th><th>Year 3</th><th>Year 4</th><th>Year 5</th><th>Year 6</th></tr>
<tr><td>Total eligible</td><td>[redacted]1</td><td>[redacted]1</td><td>[redacted]1</td><td>[redacted]1</td><td>[redacted]1</td><td>[redacted]1</td></tr>
<tr><td>Uptake rate (%)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Resistant</td><td>[redacted]1</td><td>[redacted]1</td><td>[redacted]1</td><td>[redacted]1</td><td>[redacted]1</td><td>[redacted]1</td></tr>
<tr><td>Refractory</td><td>[redacted]1</td><td>[redacted]1</td><td>[redacted]1</td><td>[redacted]1</td><td>[redacted]1</td><td>[redacted]1</td></tr>
<tr><td>Intolerant</td><td>[redacted]1</td><td>[redacted]1</td><td>[redacted]1</td><td>[redacted]1</td><td>[redacted]1</td><td>[redacted]1</td></tr>
<tr><td>Total treated</td><td>[redacted]1</td><td>[redacted]1</td><td>[redacted]1</td><td>[redacted]1</td><td>[redacted]1</td><td>[redacted]1</td></tr>
</table>
</td></tr>
<tr><td>Number of scripts</td><td>
PBS/RPBS: Given the use of ganciclovir and valganciclovir for prophylaxis reported in the Section 4 Excel workbook, where RPBS use was 0.49%, the submission assumed that no RPBS scripts would be used, thus all estimated scripts are PBS scripts.<br>
Treatment duration: The number of scripts assumed 7.5 weeks of treatment (1 script per week) sourced from SOLSTICE.<br><br>
<table>
<tr><th></th><th>Year 1</th><th>Year 2</th><th>Year 3</th><th>Year 4</th><th>Year 5</th><th>Year 6</th></tr>
<tr><td>Patients</td><td>[redacted]1</td><td>[redacted]1</td><td>[redacted]1</td><td>[redacted]1</td><td>[redacted]1</td><td>[redacted]1</td></tr>
<tr><td>PBS scripts</td><td>[redacted]2</td><td>[redacted]2</td><td>[redacted]2</td><td>[redacted]2</td><td>[redacted]2</td><td>[redacted]2</td></tr>
</table>
</td></tr>
<tr><td colspan="2">Cost of medicines</td></tr>
<tr><td>Maribavir</td><td>Requested published price: $28,209.27-per 4 packs of 28 tablets<br>Requested effective price: $[redacted] per 4 packs of 28 tablets</td></tr>
<tr><td>Substituted medicines</td><td>With no PBS-listed comparators, the submission assumed no medicines for substitution. However, the submission applied a cost offset of $11,721.23 per patient based on average cost of standard of care in the economic model. This was not reasonable as the drug cost included foscarnet and cidofovir prices that represent public hospital costs that should not be used as a cost offset, and the values used were estimated by the sponsor and may not be accurate.</td></tr>
<tr><td>Patient copayment</td><td>Copayment was calculated as $14.95 for PBS, based on scripts dispensed for ganciclovir and valganciclovir for CMV prophylaxis in calendar year 2022.</td></tr>
<tr><td colspan="2">Impact on other medicines</td></tr>
<tr><td>IAT usage</td><td>Cost offsets were based on the IAT cost generated by the economic model for initial treatment with ganciclovir, valganciclovir, foscarnet and cidofovir, including administration and monitoring costs. The submission applied a value of $11,721.23 per patient, although the value calculated by the model was $11,728.27 (cell M17 of the worksheet ‘Deterministic Results’).</td></tr>
</table>

| Component | Data source | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
| | IAT | - [redacted][3] | - [redacted][3] | - [redacted][3] | - [redacted][3] | - [redacted][3] | - [redacted][3] |
| **MBS usage and costs** | | | | | | | |
| MBS items | The submission indicated that as the monitoring requirements for maribavir are expected to be the same as that for IAT, changes to MBS items were not considered. This was reasonable. | | | | | | |

Source: Table 4.2.6, p161; Table 4.2.12, p163; Table 4.2.13, p164; Table 4.2.14, p164; Table 4.2.20, p166; Table 4.4.2, p168 of the submission.

CMV = cytomegalovirus; HSCT = haematopoietic stem cell transplant; IAT = investigator assigned treatment; SOT = solid organ transplant

*The redacted values correspond to the following ranges:*

[1] *<500*

[2] *500 to < 5,000*

[3] *Net cost saving*

6.76 The key issues with the submission's financial estimates were as follows:

- The assumed cost offset for IAT treatment was based on the cost generated by the economic model. This was not likely to be accurate. In addition, public hospital use of foscarnet and cidofovir is not a valid cost offset, resulting in the submission's financial estimates being underestimated.
- Uptake may be overestimated. The submission considered this in a sensitivity analysis.

6.77 The estimated patient numbers, prescription numbers and costs for the PBS listing of maribavir are provided in Table 19. Included is an additional analysis excluding the cost of foscarnet and cidofovir from the IAT cost offset.

**Table 19: Estimated use and financial implications**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|---|---|---|---|---|---|---|
| **Estimated extent of use** | | | | | | |
| Number of patients initiating treatment | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] |
| Number of scripts dispensed[a] | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] |
| **Estimated financial implications of maribavir** | | | | | | |
| Cost to PBS less copayments | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][4] |
| Estimated financial implications for substituted IAT | | | | | | |
| Cost to PBS less copayments | -[redacted][5] | -[redacted][5] | -[redacted][5] | -[redacted][5] | -[redacted][5] | -[redacted][5] |
| **Net financial implications** | | | | | | |
| **Net cost to PBS** | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][4] |
| Substituted IAT | -[redacted][5] | -[redacted][5] | -[redacted][5] | -[redacted][5] | -[redacted][5] | -[redacted][5] |
| **Net cost to Government** | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] |
| IAT offset excluding foscarnet + cidofovir cost | -[redacted][5] | -[redacted][5] | [redacted][5] | [redacted][5] | [redacted][5] | [redacted][5] |
| Net cost to Government | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] |

Source: Table 4.2.13, p164; Table 4.2.14, p164; Table 4.2.20, p166; Table 4.4.2, p168 of the submission.
IAT = investigator assigned treatment
[a] Assuming 7.5 weeks of treatment, based on SOLSTICE and as estimated by the submission.
*The redacted values correspond to the following ranges:*
[1] *<500*
[2] *500 to < 5,000*
[3] *$0 to < $10 million*
[4] *$10 million to < $20 million*
[5] *net cost saving*

6.78 The total cost to the PBS of listing maribavir was estimated to be $10 million to < $20 million in Year 6, and a total of $50 million to < $60 million in the first 6 years of listing. If the claimed IAT cost offsets are applied, the net cost to Government in Year 6 was estimated to be $0 to < $10 million, with a total of $30 million to < $40 million in the first 6 years of listing. Uptake may be overestimated; and cost offsets for foscarnet and cidofovir should not have been included.

6.79 When the cost of foscarnet and cidofovir were removed from IAT cost offsets, the estimated net cost to Government increased by 32% to $40 million to < $50 million over the first 6 years of listing.

6.80 Sensitivity analyses are summarised in Table 20. As indicated above, the submission presented its sensitivity analyses based on estimated net cost to the PBS for maribavir ($50 million to < $60 million over 6 years), which did not include estimated cost offsets for IAT usage.

**Table 20: Sensitivity analyses – financial estimates**

| Analysis | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|---|---|---|---|---|---|---|
| **Base case** | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][2] |
| **Uptake (base case: [redacted]% in Year 1, [redacted]% in Year 2, [redacted]% in Year 3)** | | | | | | |
| Increase by 20% | [redacted][1] | [redacted][1] | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] |
| Decrease by 20% | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] |
| **Proportion relapsed/refractory/intolerant (base case: based on North American and European literature estimates – SOT CMV infection 22.8%; RRI 37.0%; HSCT CMV infection 34.0%, RRI 57.2%)** | | | | | | |
| North American only (SOT: CMV infection 18.8%, RRI 32.6%; HSCT: CMV infection 42.5%, RRI 51.3%) | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] |
| European only (SOT: CMV infection 26.4%, RRI 40.8%; HSCT: CMV infection 26.7%, RRI 48.9%) | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] |

Source: Table 4.6.1, p169 of the submission.
CMV = cytomegalovirus; HSCT = haematopoietic stem cell transplant; IAT = investigator assigned treatment; RRI = relapsed, refractory, intolerant; SOT = solid organ transplant
*The redacted values correspond to the following ranges:*
[1] *$0 to < $10 million*
[2] *$10 million to < $20 million*

6.81 DUSC also noted the following issues with the financial estimates:

- Public hospital costs cannot be included as PBS cost offsets.
- The submission proposed maribavir is supplied with a maximum dispensed quantity of 4 packs of 28 tablets. However, the submission estimated the number of packs supplied, which overestimated the copayments paid by patients. As the dispensed maximum quantity is four, this will have slightly underestimated the cost if patients are only required to pay one copayment per four packs supplied.

Overall, DUSC considered that, after revision of these issues, the methods used to derive the utilisation and financial estimates and the structure of the estimates model were reliable for decision-making.

### *Quality Use of Medicines*

6.82 The submission stated the sponsor will support the correct use of maribavir with educational activities to ensure the population and circumstances of use are consistent with the evidence presented in the submission.

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

# 7 PBAC Outcome

7.1 The PBAC did not recommend the Section 100, Highly Specialised Drugs Program listing for maribavir for the treatment of post-transplant cytomegalovirus (CMV) infection and disease resistant, refractory or intolerant to one or more prior therapies. The PBAC considered that the comparative clinical evidence was subject to uncertainty due to the limitations of the pivotal randomised study. In addition, the

ICER was subject to a high level of uncertainty given that the economic evaluation was based on multiple assumptions that were poorly justified.

7.2 The PBAC considered the primary reason for this outcome was due to the comparative clinical evidence provided.

7.3 The PBAC noted the consumer comments and acknowledged the clinical need for effective treatments for CMV disease, which is a clear adverse prognostic factor for survival in transplant patients. The PBAC also acknowledged the clinical utility of an orally active agent to treat CMV infection, with a different side effect profile to currently available therapies.

7.4 The PBAC considered that although maribavir was proposed for second-line treatment, the wording of the restriction as proposed would allow for first-line use as the prescribing instructions defining intolerance allow for 'potential toxicity'. The Committee considered that, while it may be appropriate to allow for patients who are intolerant to first-line treatments (ganciclovir/valganciclovir) to receive maribavir, it would be appropriate to further define the patient population to ensure maribavir was not used in a first-line setting.

7.5 The PBAC considered the proposed restriction did not align with the population studied in the SOLSTICE trial, in that the trial required patients to be refractory to the most recent treatment, whether or not they were resistant or intolerant to treatment. The PBAC considered that to align the restriction with the trial, it should include the following criterion: patients must have received at least two weeks treatment with ganciclovir or valganciclovir for this infection, with virological or clinical failure.

7.6 The PBAC noted that resistance of CMV disease to current standard of care treatment is common, and as mutation testing is not currently available in Australia in a clinically useful timeframe, the only practical marker of resistance is failure of initial treatment. While the PBAC noted that, to align the restriction with the trial, the infecting CMV should also be confirmed as having genotypic resistance to ganciclovir/valganciclovir, the Committee considered it was impractical to require this as a prerequisite to use of maribavir. However, the PBAC considered that the restriction should exclude treatment with maribavir where there is evidence of genotypic resistance to maribavir, given the high rate of development of resistance to maribavir that occurs during treatment and because mutation testing may become available in the future.

7.7 The PBAC noted the SOLSTICE trial was open to patients from 12 years old (although only patients 18 years and older were enrolled) and considered that the PBS restriction should be age agnostic.

7.8 The PBAC noted that no data to support continuing treatment beyond 8 weeks was submitted, however considered that it would be appropriate for the restriction to allow for ongoing treatment beyond 8 weeks where clinically required or for retreatment where relapse has occurred, consistent with guidelines for treatment of CMV.

7.9 The resubmission proposed that the comparator was current standard of care, which it defined to include ganciclovir, valganciclovir, foscarnet and cidofovir. The PBAC noted that the existing PBS restrictions for ganciclovir/valganciclovir are for prophylaxis of CMV, and that both clinical advice and the PBS utilisation of these drugs suggest that there is substantial use of the prophylaxis listings for ganciclovir/valganciclovir for treatment of CMV disease. The Committee considered that changes to these restrictions may be required to ensure that ganciclovir/valganciclovir remain as the first-line option for patients with CMV disease, particularly if maribavir was to be listed on the PBS. The PBAC also noted that there may be some use of letermovir as an alternative treatment of CMV disease.

7.10 The PBAC noted the primary clinical evidence presented in the submission was the open-label SOLSTICE trial, where patients with CMV infections who were refractory to one or more of ganciclovir, valganciclovir, foscarnet or cidofovir, were treated with maribavir or IAT (ganciclovir or valganciclovir at standard or increased dose, or foscarnet or cidofovir based on investigator choice). The Committee noted that 46% of patients who were resistant to ganciclovir/valganciclovir were nonetheless treated with ganciclovir/valganciclovir in the IAT arm, with a switch to the 'maribavir rescue arm' being allowed after 3 weeks if patients had rising viraemia from baseline, tissue invasive CMV that became worse and rising viraemia, or if CMV viraemia was not cleared and anti-CMV treatment was necessary and there was intolerance to the IAT. The PBAC considered that number of patients who switched to the maribavir rescue arm (22) and the high rate of discontinuations in patients prior to 8 weeks in the IAT comparator arm (65.7%) potentially biased the outcomes in favour of maribavir and made it difficult to interpret the trial results.

7.11 The PBAC noted that, in SOLSTICE, CMV viraemia clearance at 8 weeks was higher in patients treated with maribavir compared to IAT (131/235 (55.7%) versus 28/117 (23.9%)) and 76/121 (62.8%) of patients who had CMV that was resistant to ganciclovir, foscarnet or cidofovir at baseline responded to maribavir at 8 weeks. The PBAC noted that maribavir resistance developed during treatment in 42 patients treated with maribavir (17.9% of all patients) and this was associated with treatment failure.

7.12 The PBAC noted that based on the NCT02927067 trial there was no significant difference between maribavir and valganciclovir in patients following HSCT. The PBAC noted that the SOLSTICE patient population was more consistent with the proposed PBS population as NCT02927067 excluded SOT patients and patients with CMV mutations conferring resistance to ganciclovir, patients must have been experiencing their first post-transplant CMV infection and patients must not have had CMV organ disease. However, the PBAC considered that the results of this trial suggested that maribavir may be inferior to valganciclovir in patients with HSCT.

7.13 The PBAC considered the SOLTICE trial suggests an advantage for maribavir in achieving clearance, however the level of benefit for maribavir was uncertain due to the high risk of bias in the open-label SOLSTICE trial, which was confounded by the

relatively high drop-out rate in the IAT arm and the extent of cross-over, and given that the results of the NCT02927067 trial in HSCT patients showed maribavir may be inferior to valganciclovir.

7.14 The PBAC acknowledged that maribavir appears to have a different safety profile compared with standard medical management, but considered that maribavir was not superior to standard medical management in terms of safety, and that a claim of non-inferior safety would be more reasonable. The PBAC noted that while there were lower rates of neutropenia and febrile neutropenia in patients treated with maribavir, the safety profile between maribavir and standard medical management was otherwise similar. The Committee additionally considered that resistance to maribavir is a significant issue.

7.15 The PBAC noted for the economic analysis the submission presented a 10-year Markov model with two stages: stage 1 from 0 to 78 weeks and stage 2 from 78 weeks to the end of the time horizon. The Committee noted that as it was based on trial outcomes up to only 8 weeks, the model relied on multiple data sources and assumptions which resulted in a high level of uncertainty in the modelled outcomes. The Committee noted that clearance and mortality data from SOLSTICE at 8 weeks were assumed to apply for 78 weeks, with no evidence to support this assumption, and that recurrence rates were modelled separately between weeks 8 to 20 and from week 21 onwards, with no justification for this separation. The Committee noted that the submission used a stage 1 length of 78 weeks based on recurrences in the OTUS study, where patient numbers were small beyond the second recurrence (4 SOT patients and 15 HSCT patients). The PBAC considered that a stage 1 length of 39.2 weeks (as used for the NICE submission) would be more appropriate as it was based on more robust data (the time frame over which the first and second recurrences happened in OTUS). The PBAC considered a 10-year model length was not justified and that the assumption that CMV-related mortality occurred beyond 78 weeks (1.5 years) was not clinically reasonable. The PBAC considered that a 2-year model length would be more appropriate. The PBAC noted that when either the stage 1 length or the time horizon were revised the ICER increased by more than 120% to over $95,000 to < $115,000/QALY, indicating a substantial level of uncertainty. Additionally, the Committee noted that drug prices for foscarnet and cidofovir were assumed, and that varying the assumed price also had a substantial impact on the ICER. Overall, the PBAC considered the model was not informative for decision making as the clinical data did not adequately support the superiority claim and because the model was based on multiple data sources and assumptions that were poorly justified.

7.16 The PBAC considered that the number of SOT and HSCT patients was reasonably well-defined, however the proportion of patients intolerant to SOC treatments, and the uptake rate for maribavir were uncertain. The PBAC noted that the submission estimated 150-300 patients per year would be treated with maribavir and considered that this appeared reasonable. However, the PBAC noted that public hospital costs, including offsets for foscarnet and cidofovir, should not be included as PBS cost

offsets. In addition, DUSC noted that the cost is slightly underestimated given the submission's use of packs supplied rather than number of scripts of 4 packs supplied.

7.17 The PBAC considered a resubmission for maribavir should provide additional data to support a clinical claim of superiority over standard of care, present a revised economic model that addresses the issues raised in paragraph 7.14 and revised financial estimates removing offsets from public hospital costs and amending the use of packs/scripts as noted in paragraph 7.15. The PBAC considered that the cost of maribavir should reflect the uncertainty in the clinical data and the short duration of efficacy in patients who develop resistance. The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

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

**Outcome:**
Not recommended

# 8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

# 9 Sponsor's Comment

The sponsor had no comment.