

## 7.03 MARIBAVIR, Tablet 200 mg, Livtency<sup>®</sup>, TAKEDA PHARMACEUTICALS AUSTRALIA PTY. LTD.

### 1 Purpose of submission

- 1.1 The Standard Re-entry submission requested Section 100 (Highly Specialised Drugs Program) Authority Required (STREAMLINED) listing for maribavir for treatment of post-transplant cytomegalovirus (CMV) infection and disease that is refractory, resistant 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 (SoC), stated to be oral valganciclovir, intravenous (IV) ganciclovir, IV foscarnet and/or IV cidofovir.

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

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: <ul style="list-style-type: none"> <li>○ Ganciclovir</li> <li>○ Valganciclovir</li> <li>○ Foscarnet</li> <li>○ Cidofovir</li> </ul>
Outcomes	<ul style="list-style-type: none"> <li>○ CMV viremia clearance (&lt;137 IU/mL)</li> <li>○ Symptom control (resolution/improvement of CMV disease/syndrome or absence of the development of CMV disease/syndrome)</li> <li>○ Treatment-emergent adverse events</li> <li>○ Treatment-emergent adverse events leading to discontinuation</li> <li>○ Health-related quality of life</li> <li>○ Maribavir resistance profile</li> <li>○ Mortality</li> </ul>
Clinical claim	Maribavir is more effective 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. Maribavir has non-inferior safety compared to standard of care.

Source: Developed during the evaluation based on table 1.2, p27 of the resubmission.

CMV = cytomegalovirus; HSCT = haematopoietic stem cell transplant; mg = milligram; mL = millilitre; IU = international unit; SOT = solid organ transplant.

Data in blue-shade are those previously seen by the PBAC.

### 2 Background

#### Registration status

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

2.2 The indication approved by the United States Food and Drug Administration (FDA) is: post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir or foscarnet. The indication approved by the European Medicines Agency (EMA) is: CMV infection and/or disease that is 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). The indications approved by the FDA and EMA are more restrictive than that approved by the TGA in that they list the specific prior therapies, and the EMA also specifies the clinical conditions for use.

**Previous PBAC consideration**

2.3 An application for the listing of maribavir in the proposed population was considered, and not recommended for listing, by the PBAC at its meeting in November 2023. A summary of the key matters of concern from the November 2023 consideration and how the resubmission addressed those concerns is presented in Table 2.

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

<b>Component</b>	<b>Matter of concern</b>	<b>How the resubmission addresses it</b>
<b>Restrictions</b>		
Clinical place in therapy	The proposed restriction did not align with the SOLSTICE population requiring patients to be refractory to most recent treatment. PBAC’s suggested criterion: patients must have received at least two weeks of ganciclovir/valganciclovir with virological or clinical failure (para 7.5, Nov 2023 PSD).	This criterion was not adopted as a clinical criterion in the resubmission. Instead, the resubmission proposed the following wording: “Patient must have a CMV infection or CMV disease that is resistant or refractory to appropriately dosed ganciclovir, valganciclovir, cidofovir or foscarnet”. To reflect the suggested restriction from the PBAC, the resubmission proposed that the definition of refractory status in the prescribing instructions section be “patients are determined to be refractory if after at least two weeks treatment of appropriately dosed ganciclovir, valganciclovir, cidofovir or foscarnet, they fail to achieve a > 1 log <sub>10</sub> decrease in CMV DNA level”. The PBAC considered this was reasonable.
Clinical place in therapy	The proposed wording could allow first-line use (as the prescribing instructions defining intolerance allow for ‘potential toxicity’) instead of intended second-line use. It would be appropriate to further define the patient population to ensure maribavir was not used in a first-line setting (para 7.4, Nov 2023 PSD).	The resubmission included a definition of intolerance, defined as Grade 3 neutropenia (absolute neutrophil count < 1000/mm <sup>3</sup> ) or impaired renal function (creatinine clearance < 50 mL/min). The PBAC considered this was reasonable.
Resistance	The restriction should exclude treatment with maribavir where there is evidence of genotypic resistance to maribavir (para 7.6, Nov 2023 PSD).	The following wording “Maribavir should not be used in patients with demonstrated resistance to maribavir” was included under the prescribing instructions.
Age	The restriction should be age-agnostic (para 7.7, Nov 2023 PSD).	Addressed, the age restriction has been removed.
Use beyond 8 weeks	The restriction should allow treatment beyond 8 weeks if clinically required, aligning with CMV treatment guidelines (para 7.8, Nov 2023 PSD).	The proposed restriction would allow for ongoing treatment beyond 8 weeks.

Public Summary Document - November 2024 PBAC Meeting

Component	Matter of concern	How the resubmission addresses it
<b>Clinical evidence</b>		
Biases in SOLSTICE's design	SOLSTICE's design had biases in favour of maribavir. High drop-out rate in the IAT arm and the extent of cross-over confounded the trial results. Additional data should be provided to support a clinical claim of superiority over SoC (para 7.10, 7.13 & 7.17, Nov 2023 PSD).	No additional data were provided in the resubmission to address this specific concern from the PBAC. The resubmission largely addressed this matter using similar justifications provided in the Pre-Sub-Committee Response (PSCR) and the pre-PBAC response submitted for the PBAC November 2023 meeting.
A safety claim	Maribavir had a different safety profile, and was not superior to SoC. A claim of non-inferior safety is more reasonable (para 7.14, Nov 2023 PSD).	The resubmission accepted the PBAC's advice of non-inferior safety to SoC.
Maribavir resistance	Maribavir resistance developed during treatment in 42 patients treated with maribavir (17.9% of all patients) and this was associated with treatment failure. Resistance to maribavir is a significant issue (para 7.11 & 7.14, Nov 2023 PSD).	Additional data from SOLSTICE were presented (Chou et al., 2024), but do not appear to address the matters raised.
<b>Economic evidence</b>		
Model structure	The model had structural issues and the presentation of the model was unnecessarily complex. The model is not likely to be reliable for decision-making, as it was informed by selective data sources and unjustified assumptions, that favoured maribavir (para 6.64, 6.51, & 7.15 Nov 2023 PSD).	The key structure of the model remained largely unchanged from the November 2023 submission.
Time horizon	10-year time horizon was not adequately justified, particularly given no CMV events were assumed to occur following 78 weeks or 1.5 years; a 2-year time horizon would be more reasonable (para 6.64, Table 14 & 7.15, Nov 2023 PSD).	The resubmission maintained the use of 10-year time horizon while presenting 2-year time horizon as a sensitivity analysis. The resubmission argued that the 10-year time horizon is conservative referring to other HTA agencies which have accepted a lifetime time horizon (47 years).
Duration of stage 1 model	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 (para 7.15, November 2023 PSD).	Addressed. The duration of the stage 1 model has been reduced from 78 weeks to 39.2 weeks.
Recurrence rates	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 (para 6.58, Nov 2023 PSD).	The resubmission maintained the use of treatment-specific recurrence. This was not justified by the evidence presented.
Retreatment duration	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 (para 6.56, Nov 2023 PSD).	The retreatment duration remained unchanged (35.98 days i.e., 5.14 weeks). Since the model assumes IAT as the retreatment for recurrence with the same CMV viremia clearance effect as in its initial SOLSTICE treatment, the 5.14-week IAT treatment duration from SOLSTICE aligns its costs with the expected effect.

Public Summary Document - November 2024 PBAC Meeting

Component	Matter of concern	How the resubmission addresses it
CMV viremia clearance effect beyond week 8 for subsequent treatment	CMV viremia clearance probabilities from week 8 to week 78 were derived from the week 8 viremia clearance 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 (para 6.58, & 7.15 Nov 2023 PSD).	Not addressed. The IAT viremia clearance effect from week 8 remained in the model and was applied to those with CMV receiving subsequent treatment. However the impact was reduced with the use of 39.2 weeks for stage 1 of the model.
Mortality data	Transition probabilities for mortality from week 8–78 were based on SOLISTICE and were classified according to response and no response 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 (para 6.58, November 2023 PSD).	The mortality assumptions remained unchanged and remained inadequately justified. However the impact was reduced with the use of 39.2 weeks for stage 1 of the model.
Utilities	The submission provided no explanation as to why Australian mapping was not used (para 6.59, November 2023 PSD).	Addressed, the utility values have been updated to include Australian specific utilities for the resubmission.
Comparator drug prices	Assumed foscarnet and cidofovir prices selected were not adequately justified (para 6.57 & 6.62 November 2023 PSD).	Not addressed. Foscarnet and cidofovir costs estimated remained inadequately justified.
Maribavir price	The cost of maribavir should reflect the uncertainty in the clinical data and the short duration of efficacy in patients who develop resistance (para 7.17, Nov 2023 PSD).	The effective DPMQ of maribavir has been reduced by █% compared to the November 2023 submission.

Source: Table 1.1, pp20-21; Table 2.1, pp60-62; Table 3.1, p134 of the resubmission.

CMV = cytomegalovirus; DPMQ = dispensed price for maximum quantity; HTA = health technology assessment; IAT = investigator-assigned treatment; mL/min = millilitres per minute; mm<sup>3</sup> = cubic millimetre; NICE = National Institute for Health and Care Excellence; Nov = November; para = paragraph; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PI = production information; PSCR = Pre-Sub-Committee Response; PSD = public summary document; SoC = standard of care

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

### 3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
<b>MARIBAVIR</b>					
maribavir 200 mg tablet, 28	Published price \$28,200.00 (public) \$28,248.37 (private) Effective price \$█ (public) \$█ (private)	4	112	1	Livtency
<b>Category / Program:</b> Section 100 – Highly Specialised Drugs Program (Public/Private/Community Access (CA)).					
<b>Prescriber type:</b> Medical practitioners					
<b>Restriction type:</b> Authority Required (Streamlined)					
<b>Administrative advice:</b> Special Pricing Arrangements apply					
<b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised					
<b>Condition:</b> Post-transplant cytomegalovirus (CMV) infection and/or disease.					

*Public Summary Document - November 2024 PBAC Meeting*

<b>Indication:</b> Acute treatment of post-transplant cytomegalovirus (CMV) infection and disease resistant, refractory or intolerant to one or more prior therapies.
<b>Clinical criteria:</b>
Patient must have received a haematopoietic 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 or refractory to appropriately dosed ganciclovir, valganciclovir, cidofovir or foscarnet
OR
Patient must have received and is intolerant to continued use of appropriately dosed ganciclovir, valganciclovir, cidofovir or foscarnet.
<b>Prescribing instructions:</b>
Patients are determined to be refractory if after at least two weeks treatment of appropriately dosed ganciclovir, valganciclovir, cidofovir or foscarnet, they fail to achieve a >1 log <sub>10</sub> decrease in CMV DNA level.
Patients are determined to be resistant by the identification of a genetic alteration that decreases susceptibility to ganciclovir, valganciclovir, cidofovir or foscarnet.
Patients are determined to be intolerant if they have Grade 3 neutropenia (absolute neutrophil count < 1000/mm <sup>3</sup> ) or impaired renal function (creatinine clearance < 50ml/min).
Maribavir should be used as monotherapy and use with valganciclovir or ganciclovir is contraindicated.
Maribavir should not be used in patients with demonstrated resistance to maribavir.
Maribavir should not be used in patients with CMV disease that involves the central nervous system.
Maribavir should not be used in patients with CMV retinitis.

- 3.1 A special pricing arrangement was requested for maribavir, with a confidential effective price of \$| for public hospitals and \$| for private hospitals (dispensed price for maximum quantity, DPMQ). Compared to the November 2023 submission, the effective DPMQ of maribavir was reduced by |% (from \$| public and \$| private) in the resubmission. The pre-PBAC response proposed a further reduction in the DPMQ of maribavir to \$| (public) and \$| (private).
- 3.2 The restriction requested in the resubmission for maribavir remained similar to that in the November 2023 submission. Key differences include:
- Removing an age criterion (patient must be ≥ 18 years old or older) to reflect the PBAC’s suggestion that the PBS restriction should be age agnostic (para 7.7, maribavir public summary document (PSD), November 2023 PBAC meeting).
  - Adding the following wording “Maribavir should not be used in patients with demonstrated resistance to maribavir” to the prescribing instructions to address the PBAC’s concern that the restriction should exclude treatment with maribavir where there is evidence of genotypic resistance to maribavir (para 7.6, maribavir PSD, November 2023 PBAC meeting).
  - Defining intolerance as Grade 3 neutropenia (absolute neutrophil count < 1000/mm<sup>3</sup>) or impaired renal function (creatinine clearance < 50 mL/min) aligning it with the contraindications specified in the product information (PI) documents for ganciclovir and valganciclovir (neutropenia) and cidofovir (impaired

renal function). The addition of this definition was to address the PBAC's concern that the previous wording in the prescribing instructions defining intolerance ('potential toxicity') would allow maribavir first-line use (para 7.4, maribavir PSD, November 2023 PBAC meeting).

- Excluding a continuation criterion to align with the PBAC's suggestion that the restriction should allow for ongoing treatment beyond 8 weeks where clinically required, or for retreatment where relapse has occurred, consistent with guidelines for the treatment of CMV (para 7.8, maribavir, PSD, November 2023 PBAC meeting). The proposed wording of the listing would not preclude use beyond 8 weeks.
- 3.3 The PBAC previously suggested that to align the restriction with the trial, the restriction 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" (para 7.5, maribavir PSD, November 2023 PBAC meeting). This wording was not adopted as a clinical criterion in the resubmission. Instead, the resubmission proposed the following criterion: "Patient must have a CMV infection or CMV disease that is resistant or refractory to appropriately dosed ganciclovir, valganciclovir, cidofovir or foscarnet". To reflect what the PBAC suggested regarding the restriction, the resubmission proposed the following definition for refractory status in the prescribing instruction: "patients are determined to be refractory if after at least two weeks treatment of appropriately dosed ganciclovir, valganciclovir, cidofovir or foscarnet, they fail to achieve a  $> 1\log_{10}$  decrease in CMV DNA level". The PBAC and the ESC agreed with the commentary that this was appropriate.
- 3.4 The resubmission has also proposed an alternative PBS restriction that does not include the intolerant patient population. The exclusion of patients with intolerance does not appear to be consistent with the PBAC's view. For example, it was noted at the November 2023 PBAC meeting that "... it may be appropriate to allow for patients who are intolerant to first-line treatments (ganciclovir/valganciclovir) to receive maribavir" (para 7.4, maribavir PSD, November 2023 PBAC meeting). The PBAC agreed with the ESC that it would be appropriate for the listing to include patients intolerant to first line treatments.
- 3.5 Overall, the PBAC considered that the revisions to the proposed restrictions in the resubmission, along with recent changes to the PBS restrictions for valganciclovir and ganciclovir (see para 5.3), had adequately addressed its previous concerns regarding the appropriate clinical place for maribavir.

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

## **4 Population and disease**

- 4.1 CMV is a common infection found in bodily fluids, often transmitted through close contact, especially with children. Infection usually occurs in childhood, with about 50%

of young adults in high-income countries being seropositive, but can occur at any age. Latent infection is lifelong. Primary infection is often asymptomatic, and even if symptomatic, immunocompetent individuals rarely become seriously ill to CMV activation. CMV can cause serious illness in immunosuppressed individuals through reactivation or primary infection. CMV disease in immunosuppressed individuals can cause fever, malaise, leukopenia, atypical lymphocytosis, or tissue-invasive disease in organs like the liver, lung, retina, brain, and colon, requiring treatment.

- 4.2 Transplant recipients are immunosuppressed and can have no CMV infection, latent infection, active infection without symptoms, or CMV disease. Transplant recipients believed to have latent CMV infection, or to be at high-risk (e.g., parents of young children) are commonly given prophylactic treatment, although maribavir has been found ineffective for use as prophylaxis. Recipients with active CMV infection but no disease are often given pre-emptive treatment, continued for at least two weeks until CMV deoxyribonucleic acid (DNA) is undetectable, though the beneficial level for treatment is not well-defined. Some CMV strains have resistant mutations in UL54 and UL97, but resistant mutations do not always lead to therapeutic failure.

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

## **5 Comparator**

- 5.1 The resubmission maintained the same main comparator as in the November 2023 submission: SoC, which includes ganciclovir, valganciclovir, foscarnet, and cidofovir.
- 5.2 The evaluation for the previous submission noted 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 ESC previously 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 (para 5.4, maribavir PSD, November 2023 PBAC meeting). Additionally, the PBAC also noted that there may be some use of letermovir as an alternative treatment of CMV disease (para 7.9, maribavir, PSD, November 2023 PBAC meeting).
- 5.3 The PBAC previously noted that the existing PBS restrictions for ganciclovir and 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 and valganciclovir for treatment of CMV disease (para 7.9, maribavir PSD, November 2023 PBAC meeting). At its March 2024 PBAC Meeting, the PBAC recommended amending the PBS restrictions for ganciclovir and valganciclovir to include the management of CMV infection in immunocompromised patients. The PBAC considered that it would be appropriate to amend the restrictions to remove reference to the prophylactic treatment phase and align the restrictions between the

drugs to provide access to SOT and bone marrow transplant patients for the management of CMV infection and disease (page 53, March 2024 PBAC meeting outcome). The PBAC also noted that ganciclovir and valganciclovir would be suitably cost-effective in the expanded population at the existing price on the basis of the evidence presented (page 53, March 2024 PBAC meeting outcome).

*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 addressed the Committee's questions regarding the relevance of the 8-week time point for assessment of relapse, noting that the 8-week time point in the trial was somewhat arbitrary and was longer than maribavir is likely to be used in clinical practice. The clinician noted that viral load would be regularly assessed and standard clinical practice would be to cease treatment after two negative results. The clinician indicated that, based on experience, in clinical practice, this is likely to be achieved after a shorter period than in the trial (closer to 4 weeks rather than 8) and is likely to be used in a similar way to existing treatments for CMV.
- 6.2 The clinician also addressed the Committee's questions regarding the patient population most likely to use maribavir, noting that it is likely to be used in patients with HSCT who have a poor neutrophil count. The clinician noted that ganciclovir and valganciclovir are not suitable in these patients and foscarnet is the alternative. The clinician noted that maribavir is most likely to be used after foscarnet in hospitalised patients, but that as foscarnet needs to be given in the hospital setting maribavir may be preferred where patients are able to be out of hospital. The clinician noted that maribavir is likely to be used less frequently in patients with SOT as ganciclovir/valganciclovir is the preferred treatment and can usually be used in these patients, without the requirement for hospitalisation.
- 6.3 The PBAC considered that the hearing was informative as it provided relevant information regarding how maribavir is currently used in clinical practice and how use in practice is likely to differ from the clinical trial.

### ***Consumer comments***

- 6.4 The PBAC noted and welcomed the input from one health care professional working in rural Australia, via the Consumer Comments facility on the PBS website. The comments described the benefits of treatment with maribavir in terms of having an alternative treatment for patients resistant to current treatment, and access to an oral treatment that can be used at home, avoiding hospital admission. The comments noted that this is particularly important in the rural setting where hospital resources are limited.

6.5 The PBAC also recalled input from health care professionals (2) regarding the previous submission. 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

6.6 The resubmission was based on one head-to-head trial comparing maribavir to investigator-assigned treatment (IAT), SOLSTICE (N = 352). This remained unchanged from the November 2023 submission. Details of the trial presented in the resubmission are provided in Table 3. Three additional publications provide information on overall mortality at 52 weeks post-maribavir (Bassel et al., 2023), drug resistance analysis in patients receiving maribavir compared to those receiving IAT (Chou et al., 2024), and healthcare resource utilisation of maribavir versus IAT in transplant recipients with CMV (Hirji et al., 2023).

**Table 3: Trial 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	<i>Clinical Infectious Diseases</i> , 2022; 75(4):690-701
	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.	
	Plus 13 abstract citations for the same trial	
	Bassel M, Romanus D, Bo T, Sundberg AK, Okala S, Hirji I. Retrospective chart review of transplant recipients with cytomegalovirus infection who received maribavir in the Phase 3 SOLSTICE trial: Data at 52 weeks post-maribavir treatment initiation.	<i>Antiviral Therapy</i> , 2023;28(5)
	Chou S, Alain S, Cervera C, Chemaly RF, Kotton CN, Lundgren J, et al. Drug Resistance Assessed in a Phase 3 Clinical Trial of Maribavir Therapy for Refractory or Resistant Cytomegalovirus Infection in Transplant Recipients.	<i>Journal of Infectious Diseases</i> , 2024;229(2):413-21.
	Hirji I, Cocks K, Moreno-Koehler A, Sundberg A. Healthcare resource utilization of maribavir versus investigator-assigned therapy in transplant recipients with cytomegalovirus infection refractory (with or without genotypic resistance) to prior treatment: Exploratory analysis of the Phase 3 SOLSTICE trial.	<i>Transpl Infect Dis</i> , 2023;25(3):e14064

Table 2.8, p69 of the resubmission.

Data in blue-shade are those previously seen by the PBAC.

6.7 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 8-week + 12-week follow-up	High	≥ 12 years <sup>a</sup> , 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 weeks, control of CMV disease, recurrence	Used in stage 1 of the model to inform clearance, recurrence and mortality transitions

Source: Table 4, maribavir, Public Summary Document, November 2023 PBAC meeting.

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

<sup>a</sup> No patients under age 18 were enrolled.

Data in blue-shade are those previously seen by the PBAC.

6.8 The PBAC previously considered that SOLSTICE had a high risk of bias, primarily due to its open-label design and the allowance for patients in the IAT arm to discontinue treatment after 3 weeks (due to lack of efficacy or toxicity) and switch to the maribavir rescue arm (para 7.10, 7.13, maribavir, PSD, November 2023 PBAC meeting). The ESC and the PBAC noted maribavir’s benefit may be overestimated due to IAT drop-outs (65.7%) and cross-over (22 patients) (paras 6.44, 7.10, maribavir PSD, November 2023 PBAC). The evaluation further noted that 3 weeks (the point at which IAT patients were permitted to discontinue and switch to maribavir) may be insufficient to assess efficacy, as IAT patients typically have longer treatment durations in practice (e.g., National Institute for Health and Care Excellence; NICE TA680, pp26-27). The Pre-Sub-Committee Response (PSCR) argued 3 weeks is sufficient time for IAT to take effect and that international guidelines indicate a minimum 2-week period is required for treatment and to help determine whether a patient is refractory/resistant to therapy. The resubmission and PSCR reiterated the arguments provided in the November 2023 submission addressing the high risk of bias, including that the open-label design was required for ethical reasons, allowing physicians to choose appropriate IAT to minimise adverse events, blinded assessment of viraemia clearance, and higher IAT discontinuation due to treatment-emergent toxicities.

### **Comparative effectiveness**

6.9 A summary of the outcomes from SOLSTICE is presented in Table 5.

Table 5: Summary of outcomes in SOLSTICE

Outcomes	Maribavir N = 235	IAT N = 117	Adjusted difference in proportion responding, maribavir – IAT (95% CI) <sup>a</sup>
CMV viremia clearance at 8 wk			
n (%)	131 (55.7%)	28 (23.9%)	<b>32.8 (22.8, 42.7)</b>
CMV viremia clearance at any time during 8 wk treatment period			
n (%)	174 (74.0%)	61 (52.1%)	<b>23.6 (13.2, 33.9)</b>
CMV viremia clearance and symptom resolution or no new symptoms at 8 wk and 16 wk			
n (%)	44 (18.7%)	12 (10.3%)	<b>9.5 (2.0, 16.9)</b>
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
New onset symptomatic CMV disease to week 20 in patients asymptomatic at baseline			
n (%)	14 (6.0%)	7 (6.0%)	NR
Recurrence of CMV viremia after clearance			
During 8 wk treatment period, n/N (%)	33/184 (17.9%)	8/61 (13.1%)	NR
After 8 wk treatment period, n/N (%)	71/184 (38.6%)	14/65 (21.5%)	NR
At any time during the study	104/184 (56.5%)	22/65 (33.8%)	NR
Median (min, max), days	42.0 (14.0, 123.0)	45.5 (16.0, 89.0)	NR
Recurrence after week 8 requiring alternative anti-CMV treatment (clinically relevant recurrence)			
n/N (%)	34/131 (26.0%)	10/28 (35.7%)	NR
Median (min, max), days	20.5 (13.0, 80.0)	22.0 (14.0, 36.0)	NR
CMV viremia clearance at 8 wk by baseline resistance to ganciclovir, foscarnet, or cidofovir			
Patients with resistant CMV responding, n/N (%)	76/121 (62.8%)	14/69 (20.3%)	NR
Patients without resistant CMV responding, n/N (%)	42/96 (43.8%)	11/34 (32.4%)	NR
CMV viremia clearance at 8 wk when maribavir RAS developed on treatment			
Patients responding with resistant CMV, n/N (%)	1/42 (2.4%)	NA	NA

Source: Table 8, maribavir, Public Summary Document, November 2023 PBAC meeting. P182 of the SOLSTICE clinical study report. 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; wk = week

**Bold** indicates statistically significant results.

Data in blue-shade are those previously seen by the PBAC.

<sup>a</sup> Adjusted for transplant type (SOT vs HSCT) and baseline CMV load.

- 6.10 The ESC previously noted that maribavir may have been less effective in patients with a higher viral load (para 6.28, maribavir PSD, November 2023 PBAC meeting). The resubmission stated that high viral load is a risk factor for poor outcomes and development of resistance to all antiviral agents. The resubmission reiterated the results from SOLSTICE emphasising that maribavir is superior compared to IAT regardless of viral load at baseline. The evaluation noted a clearance effect of 37.4% (95% confidence interval; CI: 25.41%, 49.37%) for the low viral load subgroup compared to 21.8% (95% CI: 3.93%, 39.67%) for the intermediate/high subgroup, suggesting a potential difference (noting the overlap in CI). A formal treatment by subgroup interaction analysis to test the significance of any difference was not presented in the resubmission.
- 6.11 The PBAC previously noted that maribavir resistance developed during treatment in 42 maribavir patients (17.9% of all patients) and that this was associated with

treatment failure (para 7.11, maribavir PSD, November 2023 PBAC meeting). The evaluation and the ESC previously considered that if resistance to longer term treatment developed at the same rate as seen in the trial period, efficacy would rapidly be lost (para 6.30, maribavir PSD, November 2023 PBAC meeting). The resubmission reiterated that the development of resistance in the maribavir arm did not preclude maribavir-treated patients from achieving the primary endpoint at a significantly higher proportion compared to IAT (para 6.30, maribavir PSD, November 2023 PBAC meeting). However, additional data from SOLSTICE provided in the resubmission (Chou et al., 2024) show a high incidence of resistance in non-responders (48%; 49/103) and particularly in those with viral rebound (86%; 25/29). This suggests that resistance developed during treatment and is likely a contributing factor to treatment failure. The PSCR reiterated that patients on maribavir had a longer time on treatment and a greater exposure to the drug compared to IAT, increasing the risk of resistance.

- 6.12 SOLSTICE showed that pre-specified secondary outcomes of recurrence (during 8-week treatment, after 8-week treatment, and at any time during the study) are higher with maribavir than IAT (e.g., 56.5% vs 33.8% for recurrence at any time during the study). The PSCR stated that any elevation of CMV viral load above the lower limit of quantification after confirmed viraemia clearance on 2 occasions was termed a recurrence. However, the resubmission (and the November 2023 submission) argued that these recurrence rates do not represent clinically relevant recurrence, citing the nature of CMV infection in which a latent virus reactivates during a period of immunosuppression and may not have necessitated treatment in every case. Instead, the resubmission suggested that clinically relevant recurrence would be better represented by recurrences after Week 8 which required alternative anti-CMV treatment, occurring less frequently in maribavir patients than in IAT patients (26.0% vs 35.7%). This outcome - recurrences after Week 8 requiring alternative anti-CMV treatment - was not pre-defined, it was added and analysed *post hoc* during trial completion. This analysis could be subject to bias due to factors such as investigators' decisions to modify IAT (in terms of the specific treatment given in the recurrence episode), the small number of IAT patients (28 compared to 131 maribavir patients), and potential confounding from differences in patient characteristics (among patients with recurrence). The ESC considered that clinically relevant recurrence is an appropriate end point however an 8-week timeframe is arbitrary and the *post hoc* analysis is not a robust way to assess this outcome. The ESC considered that either data on time to next treatment, or on clinically relevant viral loads, would provide more certainty that maribavir provided a benefit in reducing recurrent disease.
- 6.13 The pre-PBAC response highlighted that more patients on maribavir achieved and maintained CMV viremia clearance and symptom control through Week 16 than those on IAT and while further evidence would be helpful, no further comparative studies are available. In addition, the pre-PBAC response noted that, whilst the *post hoc* analysis is not ideal, in patients with viremia clearance at 8 weeks, the rate of recurrence requiring treatment by Week 16 was 26.0% in the maribavir group and 35.7% in the IAT group.

## Comparative harms

6.14 Key adverse events in SOLSTICE are shown in Table 6.

**Table 6: Summary of key adverse events in SOLSTICE**

Treatment-emergent adverse events	Maribavir N = 235	IAT N = 117
Deaths at any time <sup>a</sup>	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 <sup>b</sup> (%)	28/217 (12.9%)	5/103 (4.9%)
RAS developing during study conferring resistance to maribavir, n/N <sup>b</sup> (%)	42/217 (19.6%)	0

Source: Table 11, maribavir, Public Summary Document, November 2023 PBAC meeting.

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

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

<sup>b</sup> N = number of patients with baseline and post-baseline viral genotype.

Data in blue-shade are those previously seen by the PBAC.

6.15 The PBAC previously 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.

## Benefits/harms

6.16 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 (para 6.43, maribavir PSD, November 2023 PBAC meeting).

## Clinical claim

6.17 The resubmission described maribavir as superior in terms of effectiveness compared to SoC. The commentary considered the therapeutic conclusion presented in the

resubmission was not adequately supported by the clinical evidence. The PBAC previously considered that the level of benefit for maribavir was uncertain due to the high risk of bias in the open-label SOLSTICE trial, and that the 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 (para 7.10, 7.13 maribavir PSD, November 2023 PBAC). The PBAC previously suggested that a resubmission for maribavir should provide additional data to support a clinical claim of superiority over standard of care (para 7.17, maribavir PSD, November 2023 PBAC meeting). The resubmission did not present additional clinical data to address the risk of bias and therefore the magnitude of benefit of maribavir remained uncertain. The ESC agreed with the commentary that the resubmission did not address the PBAC's previous concerns and the level of benefit for maribavir remains uncertain.

- 6.18 The resubmission described maribavir as non-inferior in terms of safety compared to SoC. The resubmission accepted the PBAC's advice that a claim of superiority in terms of safety over SoC with respect to safety was not supported, and that a claim of non-inferior safety would be more reasonable (para 7.14, maribavir PSD, November 2023 PBAC meeting). The ESC considered the claim of non-inferior safety was reasonable.
- 6.19 The PBAC recalled it had previously considered that the claim of superior comparative effectiveness was not well-supported by the data. The PBAC noted that no additional clinical data were available to support the clinical claim, but considered that the outcome of recurrence requiring retreatment was likely to be clinically meaningful and the SOLSTICE trial suggested maribavir was superior to IAT for this outcome. The PBAC maintained that there was a high level of uncertainty in the magnitude of clinical benefit for maribavir due to the limitations of the trial.
- 6.20 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

### ***Economic analysis***

- 6.21 The economic evaluation remained largely unchanged from that presented in November 2023. The resubmission presented a stepped economic evaluation based on evidence from SOLSTICE, and a retrospective study of SOT and HSCT patients (TAK620-5001 and TAK620-5002; referred to as OTUS = Outcomes, Treatment Patterns and Healthcare Resource Utilization Study). Key changes included reducing the stage 1 duration from 78 to 39.2 weeks and updating the utilities analysis.

**Table 7: Summary of model structure, key inputs and rationale**

Parameter	Summary
Treatments	Maribavir vs. SoC (informed by the IAT arm of SOLSTICE) for the treatment of adults with post-transplant CMV infection and disease resistant, refractory R/R) or intolerant to one or more prior therapies.
Type of analysis	Cost-utility analysis (cost-effectiveness analysis).
Outcomes	\$/QALY and LYG.
Methods used to generate results	Markov model.
Health states	The model has been separated into two stages: Stage 1 begins with the onset of R/R CMV and includes a three state Markov model with the states being csCMV <sup>a</sup> , n-csCMV and a dead state. Stage 2 includes a two state Markov model with the states being alive or dead.
Duration of stage 1 model	39.2 weeks (78 weeks in the November 2023 submission)
Cycle length	4-week cycle length for the first 3 years, and thereafter, annual cycles.
Transition probabilities	Transition probabilities in the model are defined by three key clinical parameters: clearance, recurrence, and mortality. Clearance: SOLSTICE CSR Recurrence (clinically significant): SOLSTICE and OTUS Mortality: Week 0 to 8 – SOLSTICE IPD analysis; Week 8 to end-stage 1 – SOLSTICE IPD analysis; stage 2 – literature based, specific to SOT or HSCT.
Recurrence rates	Treatment-specific.
Health-related quality of life	Australian specific utilities based on SOLSTICE and vignette study. Resubmission: SOT: n-csCMV = 0.928, csCMV 0.729, background utility for stage 2 = 0.892 HSCT: n-csCMV = 0.826, csCMV 0.634, background utility for stage 2 = 0.864 November 2023 submission: SOT: n-csCMV = 0.834, csCMV 0.639, background utility for stage 2 = 0.808 HSCT: n-csCMV = 0.694, csCMV 0.502, background utility for stage 2 = 0.712
Time horizon	10 years.
Costs	2024 costs.

Source: Table 3.2, p135; Table 3.34, p140; Table 3.38, p168 of the resubmission.

CMV = cytomegalovirus; csCMV = clinically significant CMV infection; CSR = clinical study report; HSCT = haemopoietic stem cell transplant; IAT = investigator-assigned anti-CMV treatment; IPD = individual patient data; LYG = life year gained; n-csCMV = non-clinically significant CMV infection; QALY = quality-adjusted life year; R/R = resistant, refractory; SoC = standard of care; SOT = solid organ transplant.

Data in blue-shade are those previously seen by the PBAC.

<sup>a</sup> Patients who do not achieve CMV viremia clearance defined as plasma CMV DNA concentration <LLOQ; lower limit of quantification) or patients who in a previous cycle occupied the n-csCMV health state but then experience a clinically significant recurrence.

6.22 The resubmission largely maintained the same data sources and assumptions as used in the November 2023 submission. The PBAC previously considered the economic model for maribavir 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 (para 7.15, maribavir, PSD, November 2023 PBAC meeting).

6.23 The PBAC previously 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 (para 7.17, maribavir PSD, November 2023 PBAC meeting). In response to this, the resubmission proposed a 1% reduction of maribavir's effective price compared with the previous submission (as per paragraph 3.1). The pre-PBAC

response proposed a further reduction in the price for maribavir from \$| to \$| (weighted public/private DPMQ).

- 6.24 The ESC previously considered that the 10-year horizon used in the previous submission was inadequately justified, given no CMV events were assumed after 78 weeks and the PBAC suggested a 2-year model would be more appropriate (para 6.60, 7.15, maribavir PSD, November 2023 PBAC meeting). The resubmission maintained the 10-year time horizon, arguing it is conservative compared to lifetime horizons accepted by the Canadian Agency for Drugs and Technologies in Health (CADTH) and NICE, and citing it was used in a previous CMV prophylaxis assessment (for letermovir). While the ESC in July 2018 indicated a 10-year horizon might capture life years gained from avoiding CMV-related deaths, it noted that the extrapolations in that submission were implausible, making the results unreliable (para 6.46, letermovir PSD, July 2018 PBAC meeting). The PBAC considered that the 10 year time horizon was inappropriate given the high level of uncertainty in the trial outcomes and lack of long term data to inform the modelled outcomes. The PBAC recalled that it previously considered that a 2-year model length would be more appropriate (para 7.15, maribavir PSD, November 2023 PBAC meeting).
- 6.25 The PBAC previously 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 (para 7.15, maribavir PSD, November 2023 PBAC meeting). The duration of the stage 1 model was reduced from 78 weeks to 39.2 weeks in the resubmission. The ESC noted that the issue of the duration for which the observed data for clearance and mortality can be applied in the model has not been addressed in the submission as no additional longer-term data were applied in the model. However, the ESC considered the reduction in the duration of stage 1 of the model was appropriate and mitigates the impact of uncertainty from applying the short term observed data on clearance and mortality beyond the trial period.
- 6.26 The resubmission maintained the use of treatment-specific recurrence rates as higher in the IAT group compared to maribavir, arguing this was supported by the outcome of recurrence requiring alternative treatment. There was insufficient evidence in the resubmission to support the higher rates of recurrence in IAT (see paragraph 6.12). The ESC previously considered that the submission did not adequately justify the use of treatment-specific recurrence from SOLSTICE while the PBAC noted that the model accepted by NICE was based on treatment independent recurrence (para 6.58, 7.15, maribavir PSD, November 2023 PBAC meeting). The ESC reiterated its view that the use of treatment-specific recurrence rates was not adequately justified by the trial data. In the pre-PBAC response the sponsor accepted this change to the model for the revised base case.
- 6.27 The resubmission maintained the approach used in November 2023 to estimate the cost of foscarnet, citing it is based on the pricing research conducted internally by the Sponsor. The ESC previously noted that the assumed prices for foscarnet (and cidofovir), were funded through state-level tenders or hospital purchases and were

inadequately justified (para 6.57, 6.62, maribavir, PSD, November 2023 PBAC meeting). The ESC and PBAC noted that the most appropriate prices for foscarnet and cidofovir for application in the model remain uncertain.

6.28 The evaluation considered the cost of foscarnet was likely to be overestimated due to the following reasons:

- The evaluation considered the dose of foscarnet used in the model was overestimated. While the guidelines quoted in the resubmission<sup>1</sup> recommend an initial regimen of 60 mg/kilogram 3 times per day over 2–3 weeks, followed by once daily maintenance dose, the model applied a frequency of 3 times per day for the extended duration of a full 28 day-cycle (i.e., full of 4-week cycle). The PSCR argued that the method for estimating the use of foscarnet in the resubmission is reflective of the dosing regimen patients would receive in clinical practice, and stated that Australian clinical experts have noted that in practice, patients would receive a single dosing regimen until the CMV is cleared. The ESC noted that the dose of foscarnet in Australian guidelines is 90 mg/kg every 12 hours<sup>2</sup>, which would be equivalent in cost to 60 mg/kg 3 times per day (as used in the resubmission), but costs would be lower if maintenance dosing is used. The PBAC noted that input from the clinician at the sponsor hearing indicated that patients would be treated with the single dose regimen with a view to achieving full clearance.
- The evaluation considered the duration of treatment for foscarnet was overestimated. The model applied the mean duration of treatment from IAT of 5.14 weeks for foscarnet, longer than its exposure duration in SOLSTICE of 4.63 weeks.

6.29 The ESC considered that applying the average IAT exposure duration of 5.14 weeks to all SoC drugs was inappropriate as the model is sensitive to the assumed duration of treatment for each IAT drug because differences in the costs for each IAT drug are substantial. As foscarnet is the most expensive IAT drug and accounts for a substantial proportion of IAT use (43.5% based on SOLSTICE), overestimation of its cost results in an overestimate of the IAT cost. The sponsor applied treatment-specific exposure durations to the model for the revised pre-PBAC response base case.

6.30 The evaluation considered the assumption in the resubmission that IAT costs and CMV viremia clearance at week 8 would apply to those receiving retreatment for recurrence was inadequately justified.

---

<sup>1</sup> NICE. British National Formulary (BNF) 2023 [Available from: <https://bnf.nice.org.uk/>].

<sup>2</sup> Therapeutic Guidelines. Cytomegalovirus (CMV) infection tglcdp-tg-org-au: Therapeutic Guidelines; 2019 [Available from: [https://taldcdp-tg-org-au.ezproxy.library.sydney.edu.au/viewTopic?etqAccess=true&guidelinePage=Antibiotic&topicfile=bartonella-infections&guidelinename=auto&sectionId=r\\_abq16-c21-ref1#r\\_abq16-c21-ref1](https://taldcdp-tg-org-au.ezproxy.library.sydney.edu.au/viewTopic?etqAccess=true&guidelinePage=Antibiotic&topicfile=bartonella-infections&guidelinename=auto&sectionId=r_abq16-c21-ref1#r_abq16-c21-ref1)].

- 6.31 In terms of the proportion of IAT use, the PSCR stated that the treatment in the model is consistent with what was presented in the SOLSTICE trial. However, the trial did not capture the proportion of IAT drugs in retreatment and ESC noted that the proportion of use of IAT drugs is uncertain. The pre-PBAC response argued that by assuming the same proportion of valganciclovir and ganciclovir use in retreatment as in initial treatment, the model potentially underestimates the use of foscarnet because there is likely to be a higher proportion of foscarnet use where patients previously failed valganciclovir. However, the 43.5% of patients who received foscarnet as the initial treatment in the SOLSTICE trial would also be less likely to be re-treated with foscarnet, so assuming the same proportion of valganciclovir and ganciclovir use in retreatment is not necessarily conservative.
- 6.32 The PBAC previously noted that no evidence was provided to support the use of CMV viremia clearance at week 8 from IAT being applied up to week 78 by the November 2023 submission (paras 6.58, 7.15, maribavir PSD, November 2023 PBAC meeting). The ESC also previously considered that assuming the IAT treatment duration from SOLSTICE (5.14 weeks or 35.98 days) was unlikely to represent actual treatment duration, which may vary across recurrence events (para 6.56, maribavir PSD, November 2023 PBAC meeting). The evaluation further noted that assuming the retreatment IAT clearance effect to be the same as at week 8 in SOLSTICE is inherently uncertain, affected by the risk of bias in assessing the IAT effect from SOLSTICE. Applying the same viremia clearance effect over time is unrealistic, as drug resistance may dilute the clearance effect. Additionally, applying this assumption to all patients not achieving CMV clearance does not reflect the evidence from SOLSTICE wherein a substantial proportion of IAT patients discontinued before completing 8 weeks of treatment (79/117; 65.7%) and information regarding their subsequent treatment is unknown. Overall, the ESC considered that the modelled costs and effects for retreatment were highly uncertain.
- 6.33 A summary of the disaggregated and aggregated results for resource items is presented in Table 8.

Table 8: Health care resource items: disaggregated summary of cost impacts

	Maribavir	SoC	Increment	% of total incremental cost
<b>Initial treatment (proposed drug and comparator)</b>	<b>\$</b>	<b>\$11,746</b>	<b>\$</b>	<b>%</b>
Total acquisition costs	\$	\$7,808	\$	
Total administration costs	\$0	\$2,981	-\$2,981	
Total monitoring costs	\$1,113	\$957	\$156	
<b>Subsequent treatment (retreatment) costs</b>	<b>\$</b>	<b>\$21,636</b>	<b>-\$</b>	<b>-%</b>
Total acquisition costs	\$	\$14,171	-\$	
Total administration costs	\$3,770	\$5,411	-\$1,640	
Total monitoring costs	\$1,431	\$2,054	-\$623	
<b>Total health resource utilisation</b>	<b>\$11,284</b>	<b>\$13,807</b>	<b>-\$2,523</b>	<b>-42.51%</b>
Hospitalisations	\$11,284	\$13,807	-\$2,523	
<b>Total adverse events</b>	<b>\$8,897</b>	<b>\$11,890</b>	<b>-\$2,993</b>	<b>-50.43%</b>
<b>Total graft loss</b>	<b>\$3,154</b>	<b>\$3,602</b>	<b>-\$448</b>	<b>-7.55%</b>
Heart	\$352	\$401	-\$50	
Kidney	\$1,921	\$2,194	-\$273	
Lung	\$714	\$816	-\$101	
Liver	\$76	\$87	-\$11	
Other	\$91	\$103	-\$13	
<b>Total costs</b>	<b>\$</b>	<b>\$62,681</b>	<b>\$</b>	<b>%</b>

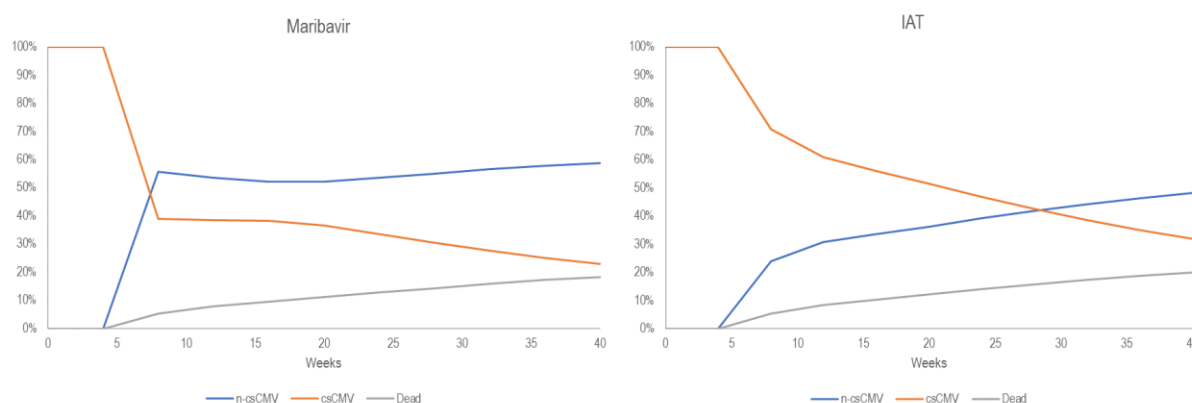
Source: Table 3.64, p186 of the resubmission.

SoC = standard of care

6.34 The model estimated a subsequent treatment cost for SoC of \$21,636 which is higher than for maribavir at \$, and accounts for the largest cost offset estimated by listing maribavir (-%). This estimate is uncertain given the overestimated duration of use of foscarnet inflating subsequent treatment costs in both maribavir and SoC in the resubmission base case. However, given a higher proportion of patients with clinically significant CMV infection (csCMV) in SoC than maribavir, it disproportionately impacts SoC more than maribavir. Overall, the cost offsets from subsequent treatments are likely overestimated in favour of maribavir.

6.35 A summary of the model traces over time for maribavir and IAT for stage 1 is presented in Figure 1.

Figure 1: Markov traces between maribavir and IAT for stage 1.



Source: sheet 'Deterministic Results' of the economic Excel model  
csCMV = clinically significant CMV infection; n-csCMV = non-clinically significant CMV infection

- 6.36 The model predicts that patients with non-clinically significant CMV infection (n-csCMV) would account for 55.7% of maribavir patients and 23.9% of IAT patients at week 8, consistent with CMV viremia clearance effect observed at week 8 in SOLSTICE. After that, the model predicts an increase in patients with n-csCMV up to the end of stage 1 period for both maribavir and IAT. However, this constant improvement in patients with CMV viremia clearance over time is unlikely, considering that resistance is likely to develop. Thus, the model likely overestimated the clearance benefits in both the maribavir and IAT arms during the post-trial period. In terms of effect, this appeared to favour IAT; however, whether the model truly favours IAT depends on whether this effect outweighs the likely overestimate of IAT costs in the model.
- 6.37 The resubmission provided revised utility values using an Australian specific tariff (Norman et al., 2023) for EQ-5D-5L data from SOLSTICE and vignette studies presented in the previous submission. The updated utility values are all higher than those in the November 2023 submission (see Table 7). In addition, the utility values, especially the value of 0.928 applied for SOT patients with CMV viremia clearance during stage 1 (non-csCMV state) and the value of 0.864 background utility applied for HSCT patients during stage 2, are relatively high compared to the Australian norm (e.g., 0.86 by Redwood et al., 2024). The ESC previously noted that the utility values for post-transplant and CMV infection patients, both 0.9, in the letermovir submission appeared implausibly high, considering that these patients were considerably unwell (para 6.35, 6.38, and 6.42, letermovir PSD, July 2018 PBAC meeting). The ESC agreed with the commentary that the updated utility values appear implausibly high and noted that it was unclear whether the decrement values for csCMV were from the updated analysis. The ESC noted that applying the utility values from the November 2023 submission increased the ICER to \$55,000 to < \$75,000 per QALY (1% increase).
- 6.38 A summary of the key drivers of the model is presented in Table 9.

Public Summary Document - November 2024 PBAC Meeting

Table 9: Key drivers of the model

Description	Method/Value	Impact Base case: \$ [redacted] /QALY gained.
Maribavir's clearance effect	Maribavir's clearance effect at week 8 was considered uncertain and likely overestimated.	Moderate-high, favours maribavir. Reduce maribavir's clearance effect by [redacted]% the ICER to \$ [redacted] /QALY gained.
Foscarnet's proportion in subsequent treatment	Foscarnet accounts for 43.5% of retreatment IAT.	Moderate-high, favours maribavir. Reducing its use by [redacted]% increased the ICER to \$ [redacted] /QALY gained.
Recurrence	Treatment-specific recurrence (higher in IAT than maribavir) not supported by evidence.	Moderate-high, favours maribavir. Use of treatment-independent recurrence increased the ICER to \$ [redacted] /QALY gained.
Foscarnet's duration	Overestimate use of foscarnet duration.	Moderate, favours maribavir. Use of individual IAT duration of treatment of increased the ICER to \$ [redacted] /QALY gained.

Source: compiled during the evaluation.

IAT = investigator-assigned treatment; ICER = incremental cost effectiveness ratio; 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

6.39 A summary of the results from the economic model is presented in Table 10.

Public Summary Document - November 2024 PBAC Meeting

Table 10: Results of the stepped economic evaluation

Step and component	Maribavir	SoC	Increment
<b>Step 1: Trial-based costs and outcomes at 8 weeks</b>			
Costs	\$	\$13,216	\$
Responder (clearance)	55.70%	23.90%	31.80%
Incremental cost/responder			1
<b>Step 2: Time horizon extended to 39.2 weeks</b>			
Costs	\$	\$56,348	\$
LY	0.62	0.61	0.01
Incremental cost/extra LY gained			2
<b>Step 3: Time horizon extended to 10 years</b>			
Costs	\$	\$62,681	\$
LY	4.90	4.81	0.09
Incremental cost/extra LY gained			1
<b>Step 4: Utility weights applied</b>			
Costs	\$	\$62,681	\$
QALYs	4.28	4.17	0.11
Incremental cost per QALY gained (base case)			3
<b>November 2023 submission</b>			
Step and component	Maribavir	SoC	Increment
<b>Step 1: Trial-based costs and outcomes at 8 weeks</b>			
Costs	\$	\$17,609	\$
Responder (clearance)	55.70%	23.90%	31.80%
Incremental cost/responder			1
<b>Step 2: Time horizon extended to 78 weeks</b>			
Costs	\$	\$81,897	\$
LY	1.18	1.16	0.02
Incremental cost/extra LY gained			4
<b>Step 3: Time horizon extended to 10 years</b>			
Costs	\$	\$82,886	\$
LY	4.69	4.56	0.13
Incremental cost/extra LY gained			1
<b>Step 4: Utility weights applied</b>			
Costs	\$	\$82,886	\$
QALYs	3.52	3.39	0.13
Incremental cost per QALY gained (base case)			3

Source: Table 3.62, p184 of the resubmission.

LY = life year; QALY = quality adjusted life year; SoC = standard of care

Data in blue-shade are those previously seen by the PBAC.

The redacted values correspond to the following ranges:

1 \$55,000 to < \$75,000

2 > \$1,055,000

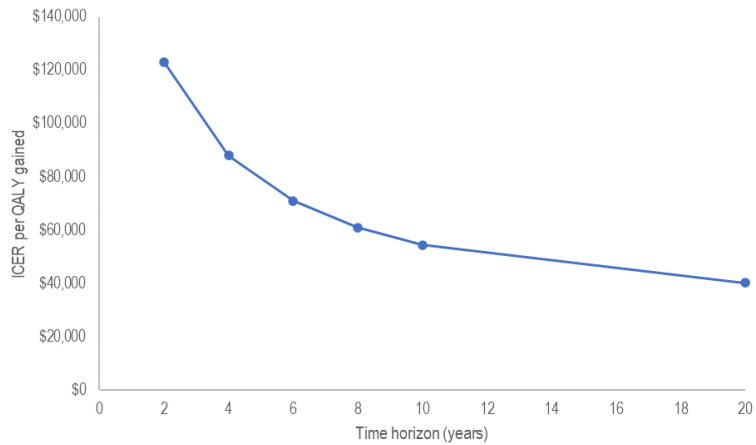
3 \$45,000 to < \$55,000

4 \$255,000 to < \$355,000

6.40 The incremental cost effectiveness ratio (ICER) in the resubmission was estimated at \$45,000 to < \$55,000 per QALY gained, slightly increased from the November 2023 submission of \$45,000 to < \$55,000 per QALY gained.

6.41 A trace of the ICER over time horizon is presented in Figure 2.

Figure 2: A trace of the ICER over time horizon



Source: compiled during the evaluation using the economic Excel model provided by the resubmission.  
ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year

6.42 Results from key sensitivity analyses are summarised in Table 11.

Table 11: Sensitivity analyses

Analyses	Inc. cost (\$)	Inc. QALY	ICER	%change
<b>Base-case</b>		0.11	1	-
Time horizon (base case: 10 years)				
2 years		0.05	2	+ %
Discount rate (base case: 5%)				
0.0%		0.13	1	%
3.5%		0.11	1	%
Clearance effect (base case: at week 8)				
Reduction in maribavir's effect by 5%		0.10	3	+ %
Reduction in maribavir's effect by 10%		0.09	4	+ %
Difference at any time during 8-week period <sup>a</sup>		0.06	5	+ %
Recurrence (base case: treatment-specific: IAT has higher recurrence)				
Treatment-independent		0.10	3	+ %
Retreatment distribution (base case: vgcv 25.4%, gcv 25.9%, fos 43.5%, cdv 5.2%)				
Reducing share of foscarnet by 50% (vgcv 35.2%, gcv 35.9%, fos 21.8%, cdv 7.2%)		0.11	3	+ %
Duration of IAT (base case: mean IAT of 5.14 wks)				
Individual IAT duration		0.11	3	+ %
Foscarnet's dose (base case: 60mg TID)				
60 mg TID for 2 wks + 60 mg QD maintenance		0.11	4	+ %
60 mg TID for 3 wks + 60 mg QD maintenance		0.11	3	+ %
Utility (base case: updated analysis)				
Values used in the November 2023 submission		0.10	3	+ %
<b>Multivariate analyses</b>				
A: Individual IAT duration + AND foscarnet's dose 60 mg TID for 2 wks + 60 mg QD maintenance		0.11	4	%
B: A + Treatment-independent recurrence		0.10	2	%
C: B + 2-year time horizon		0.04	6	%
<b>Multivariate analyses conducted for ESC</b>				
D: Individual IAT duration and treatment-independent recurrence		0.10	4	%
E: D + reducing share of foscarnet by 50%		0.10	7	%

Source: Table 3.72, p191 of the resubmission; compiled during the evaluation using the economic Excel model provided by the resubmission.

cdv = cidofovir; fos = foscarnet; gcv = ganciclovir; IAT = investigator-assigned anti-CMV treatment; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; QD = once a day; TID = three times per day; vgcv = valganciclovir; wks = weeks.

<sup>a</sup> based on the difference in CMV viremia clearance observed at any time during 8 weeks treatment period (see Table 5) as compared with the base case analysis which used the difference at 8 weeks.

The redacted values correspond to the following ranges:

- 1 \$45,000 to < \$55,000
- 2 \$115,000 to < \$135,000
- 3 \$55,000 to < \$75,000
- 4 \$75,000 to < \$95,000
- 5 \$155,000 to < \$255,000
- 6 \$255,000 to < \$355,000
- 7 \$95,000 to < \$115,000

6.43 The model was highly sensitive to the clearance effect of maribavir at week 8 (the primary endpoint in SOLSTICE). A 5% reduction in this effect increased the ICER by % (to \$55,000 to < \$75,000 per QALY). Assuming the effect is the same as the difference observed in the proportion who experienced viremia clearance at any time during the 8-week treatment period increased the ICER by % (to \$155,000 to < \$255,000 per QALY). The pre-PBAC response acknowledged that the uncertainty in the clinical

efficacy is partially driven by the significant drop out rate in the IAT arm of the trial. Additionally, the model was sensitive to assumptions regarding recurrence, and the estimates of IAT and subsequent treatment costs, which are primarily influenced by the estimated use of foscarnet.

- 6.44 The ESC noted that a multivariate analysis that included individual IAT duration and treatment independent recurrence rates resulted in an ICER of \$75,000 to < \$95,000 per QALY. Reducing the proportion of foscarnet retreatment use in IAT by 50%, in addition to these inputs, resulted in an ICER of \$95,000 to < \$115,000 per QALY.
- 6.45 The pre-PBAC response proposed a revised base case, in which treatment agnostic recurrence rates and individual IAT drug treatment durations were applied, and with the reduced proposed price for maribavir (\$ weighted public/private DPMQ). This resulted in an ICER of \$55,000 to < \$75,000. The PBAC noted that when the share of foscarnet in retreatment was reduced by 50% and the time horizon reduced to 2 years, the ICER increased to \$155,000 to < \$255,000 per QALY.
- 6.46 The PBAC noted that input from the sponsor hearing, from a clinician experienced in the use of maribavir, indicated that the treatment duration in the SOLSTICE trial is unlikely to reflect its use in clinical practice. The PBAC noted the advice that response to maribavir is likely to be assessed frequently and use is likely to be similar to other treatments for CMV. Noting that the model assumed 7.5 weeks of maribavir treatment, and 5.14 weeks (average) for IAT, the PBAC considered that treatment costs for maribavir are likely to be overestimated in the model as they were driven by the 8-week trial design. The PBAC noted that the ICER was sensitive to the treatment duration for maribavir and when the duration was reduced to that of valganciclovir (5.64 weeks, the longest of IAT) in the more conservative analysis (as per paragraph 6.45) the ICER was reduced from \$155,000 to < \$255,000 per QALY to \$5,000 to < \$15,000 per QALY.

### ***Drug cost/patient/course***

- 6.47 A summary of the drug costs per patient for maribavir and IAT is presented in Table 12. The estimates are based on the available data from the fixed 8-week treatment course in SOLSTICE. The evaluation noted that the total cost per course shown is likely an underestimate where extended or repeated courses of treatment (for maribavir or IAT) might be necessary. However, the PBAC also noted that the fixed 8-week treatment course in SOLSTICE was longer than maribavir and IATs are likely to be used in practice. Therefore, although repeated courses have not been accounted for, drug costs per patient per course are likely to be overestimated.

Table 12: Drug cost per patient for maribavir and IAT

Component	Maribavir			IAT			Financial estimates
	Trial	Model	Financial estimates		Trial	Model	
Mean dose	Not reported	400 mg BID	400 mg BID	Ganciclovir	Not reported	5 mg/kg BID	Not estimated
				Valganciclovir		900 mg q12h	
				Foscarnet		60 mg/kg TID	
				Cidofovir		5 mg/kg qwk	
Mean duration (weeks)	6.91	7.5	7.5	Ganciclovir	4.54	5.14	
				Valganciclovir	4.78	5.14	
				Foscarnet	4.46	5.14	
				Cidofovir	3.70	5.14	
Cost/patient/week	\$█	\$█	\$█	Ganciclovir	\$258	\$258	
				Valganciclovir	\$112	\$112	
				Foscarnet	\$3,142	\$3,142	
				Cidofovir	\$1,097	\$1,097	
Cost/patient/course	\$█	\$█	\$█	Weight	gcv 25.4%, vgcv 25.9%, fos 43.5%, cdv 5.2%		
					\$6,744	\$7,803	

Source: Compiled during the evaluation; sheet 'Drug Costs (Raw)' of the economic model; Table 14.3.7.1.1.1, p4076, the SOLSTICE's clinical study report.

BID = twice daily; cdv = cidofovir; fos = foscarnet; gcv = ganciclovir; IAT = investigator assigned treatment; q12h = every 12 hours; qwk = once weekly; TID = 3 times daily; vgcv = valganciclovir.

Note: as the mean dose in trial is not reported, the mean dose (recommended dose) used in the economic model is used to estimate drug cost for the trial estimate

6.48 The estimates for the trial dose and duration for both maribavir and IAT (\$█ for maribavir; and \$6,744 for IAT) are lower than that for the economic and financial models (\$█ for maribavir; and \$7,803 for IAT from the economic model). This is primarily because the actual treatment duration in SOLSTICE for each IAT drug is shorter than that used in the economic model. Costs for within trial exposure are based on recommended dosing as the actual mean doses were not available; use of mean doses is likely to have resulted in lower costs per course for both maribavir and IAT. Overall, the drug cost per patient per treatment course in the economic model is overestimated compared to the actual costs observed in SOLSTICE.

6.49 The ESC noted that the costs for anti-CMV treatments are in the context of costs for transplants of around \$58,000 (kidney) up to \$222,000 (heart).

### **Estimated PBS usage & financial implications**

6.50 This submission was not considered by DUSC. The resubmission applied an epidemiological approach to the financial estimates. The methods for estimating the utilisation and financial implications to Government remain largely unchanged from the November 2023 submission, noting the use of more recent population data. The key difference from the November 2023 submission is that the resubmission included patients below 18 years of age to reflect the PBAC's advice on an age agnostic listing (para 7.7, maribavir PSD, November 2023 PBAC meeting). The DUSC previously commented on the data sources and parameter values used in the financial estimates of the November 2023 submission and considered them broadly reasonable (Drug

Public Summary Document - November 2024 PBAC Meeting

Utilisation Sub Committee: Advice to PBAC, maribavir, November 2023 PBAC meeting). A summary of key inputs for financial estimates is presented in Table 13.

**Table 13: Key inputs for financial estimates**

Parameter	Value applied and source	Comment
Incident patients	SOT Yr 1: 1,817 based ANZOD registry (data up to 2022) and ANZDATA registry (data up to 2022) with a yearly growth rate of 3.86%. HSCY Yr 1: 730 based on ANZDATA registry (2013-2023 annual reports), with a yearly growth rate of 4.38% based on the registry.	The ESC agreed with the commentary that this data source was reasonable and provided robust estimates of the annual number of transplant patients.
CMV infection, refractory, resistant, and intolerant patients	SOT CMV infection: 22.8% (35 studies); Refractory to SoC: 21.7% (5 studies); Resistant to SoC: 5.3% (16 studies); Intolerant to SoC: 10.0% (OTUS assumption). HSCY CMV infection: 34.0% (35 studies); Refractory to SoC: 32.0% (8 studies); Resistant to SoC: 5.2% (13 studies); Intolerant to SoC: 20.0% (OTUS assumption).	Unchanged from the previous submission. The PBAC and the DUSC noted no major issues.
Uptake rate	Yr 1: █%, Yr 2: █%, Yr 3: █%, Yr 4 to Yr 6: █% based on assumption.	Unchanged from the November 2023 submission. The PBAC previously noted that the proportion of patients intolerant to SoC treatments was uncertain (para 7.16, maribavir PSD, November 2023 PBAC meeting).
Duration of treatment	7.5 weeks based on the exposure duration from SOLSTICE.	Unchanged from the November 2023 submission. The duration derived from fixed 8-week treatment duration might not reflect practice.  The 7.5-week treatment duration is based on the exposure duration in SOLSTICE and was slightly higher than its actual duration (6.91 weeks or 92.1% compliance).
Dose	400mg BID, recommended dose in SOLSTICE	Reasonable

Source: Table 4.1, p195, Table 4.3, p198, Table 4.5, p199, Table 4.10, p201, Table 4.12, p202, Table 4.13, p202, Table 4.19, p205, Table 4.22, p206, Table 4.29, p209; Figure 2, p124, Table 14.3.7.1.1.1, p4076, of the SOLSTICE's clinical study report; DRUG UTILISATION SUB-COMMITTEE: ADVICE TO PBAC, maribavir, November 2023 PBAC meeting.

BID = twice daily; CMV = cytomegalovirus; DUSC = Drug Utilisation Sub Committee; HSCT = haematopoietic stem cell transplant; PBAC = Pharmaceutical Benefits Advisory Committee; PSD = public summary document; SoC = standard of care; SOT = solid organ transplant; Yr = year

Data in blue-shade are those previously seen by the PBAC.

6.51 The PBAC considered the assumed 7.5 weeks of treatment may not reflect clinical practice; although some patients may require longer treatment, clinical experience with maribavir (as per the sponsor hearing) suggests that patients are likely to be monitored closely and treated until clearance, resulting in shorter durations than in SOLSTICE for many patients. In addition, the actual duration of treatment in SOLSTICE was 6.91 weeks when compliance was accounted for. While patients may need retreatment for recurrence, this was not accounted for in the financial estimates or in the economic model.

Public Summary Document - November 2024 PBAC Meeting

- 6.52 The resubmission did not present an estimation of changes in use and the financial impact of other medicines. While the resubmission noted the PBAC’s recent recommendation for valganciclovir and ganciclovir for the same restriction requested in the resubmission (page 53, March 2024 PBAC meeting outcome), it stated that the changes to the PBS listing had not yet occurred making it challenging to determine the impact of maribavir on these medicines. The potential reduction in use of valganciclovir and ganciclovir resulting from the listing of maribavir may lead to an overestimated net cost to the PBS for maribavir. However, this impact is likely minimal due to the comparatively low cost of these medicines on the PBS.
- 6.53 The use of foscarnet is likely to decrease with the listing of maribavir, reducing the need for infusion drug administration (Medicare Benefits Schedule; MBS item 13950). The financial implications of this reduction were not estimated in the resubmission.
- 6.54 A summary of the estimated use and financial implications is presented in Table 14.

**Table 14: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated	1	1	1	1	1	1
Number of scripts dispensed	1	1	2	2	2	2
<b>Estimated financial implications of maribavir</b>						
Cost to PBS less copayments (\$)	3	3	3	3	3	3
<b>Net financial implications</b>						
Net cost to PBS (\$)	3	3	3	3	3	3
<b>Previous November 2023 submission</b>						
Net cost to PBS (\$)	3	3	3	3	3	3
<b>PBAC revised estimated extent of use<sup>a</sup></b>						
Number of patients treated	1	1	1	1	1	1
Number of packs dispensed	1	1	1	1	1	1
<b>Estimated financial implications of maribavir</b>						
Cost to PBS less copayments	3	3	3	3	3	3

Source: Table 4.22, p206; Table 4.38, p213; Table 4.36, p212 of the resubmission.

PBS = Pharmaceutical Benefits Scheme

The resubmission assumed no RPBS scripts would be used as in the November 2023 submission, given ganciclovir and valganciclovir prophylaxis for RPBS is <1%.

Data in blue-shade are those previously seen by the PBAC.

<sup>a</sup> Revision of the duration of maribavir treatment to 5.64 weeks, revision of the DPMQ for maribavir to \$█ (public hospital) and \$█ (private hospital) as per pre-PBAC response.

The redacted values correspond to the following ranges:

1 <500

2 500 to < 5,000

3 \$0 to < \$10 million

- 6.55 The total cost to the PBS of listing maribavir was estimated to be \$0 to < \$10 million in year 6, and a total of \$40 million to < \$50 million in the first 6 years of listing in the resubmission. When the treatment duration was revised from 7.5 to 5.64 weeks, consistent with PBAC’s consideration of treatment duration in the economic evaluation, script numbers decreased to < 500 in year 1 to < 500 in year 6. With application of the reduced price for maribavir, the total cost was estimated to be \$0 to < \$10 million in Year 6, and a total of \$30 million to < \$40 million in the first 6 years of listing.

- 6.56 The PBAC considered there remains uncertainty regarding both the length of treatment and the proportion of patients requiring retreatment.

### **Quality Use of Medicines**

- 6.57 The resubmission stated that 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 resubmission.

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

- 6.58 The pre-PBAC response stated that the sponsor does not see a need for a risk-sharing arrangement (RSA). The PBAC considered that an RSA, with expenditure caps, would be required to mitigate the risk of a longer duration of treatment with maribavir, or frequent retreatment with maribavir, which would impact on the cost-effectiveness of maribavir. The PBAC considered that the financial estimates, with revisions as per paragraph 6.55, would be a reasonable basis for calculation of the expenditure caps.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the listing of maribavir, for the treatment of post-transplant CMV infection and disease that is resistant, refractory or intolerant to one or more prior therapies, on the basis that it should be available only under special arrangements under Section 100 (HSD). The PBAC was satisfied that maribavir provides, for some patients, a significant improvement in efficacy over SoC (including ganciclovir, valganciclovir, cidofovir and foscarnet). The PBAC recalled that it previously considered the comparative clinical evidence was subject to uncertainty due to the limitations of the pivotal randomised study. The PBAC noted that no additional data were available to address this uncertainty, but notwithstanding its limitations, maintained that the SOLTICE trial suggests an advantage for maribavir in achieving viral clearance. The PBAC noted that the resubmission addressed some areas of uncertainty in the economic evaluation, though a high level of uncertainty remained, largely due to the lack of long-term data. The PBAC considered that the treatment duration for maribavir appeared to be overestimated in the economic evaluation and noted that the evaluation was sensitive to this value. Although the treatment duration of maribavir in clinical practice is uncertain, additional analyses with reduced treatment duration provided reasonable assurance that maribavir would be cost effective at the price proposed in the pre-PBAC response.
- 7.2 The PBAC noted the consumer comments and acknowledged the clinical need for effective treatments for CMV disease, and the clinical utility of an orally active agent to treat CMV infection, with a different side effect profile to currently available therapies. The PBAC considered that there was a clinical need for additional treatment options for patients with disease resistant to available therapies.

- 7.3 The PBAC considered that the revisions to the proposed restrictions in the resubmission had adequately addressed its previous concerns regarding the appropriate clinical place for maribavir. Specifically, the revised restrictions appropriately: removed the age criterion, added wording to prescribing instructions to exclude treatment with maribavir where there is evidence of genotypic resistance, adequately defined intolerance and refractoriness to other treatments, and allowed ongoing treatment beyond 8 weeks and retreatment where relapse has occurred.
- 7.4 The comparator proposed in the resubmission remained standard of care, which was defined to include ganciclovir, valganciclovir, foscarnet and cidofovir. The PBAC considered that this was appropriate. The PBAC noted that changes to the PBS restrictions for valganciclovir and ganciclovir would help to ensure that they remained the first line option for treatment of CMV disease. While foscarnet was a relevant comparator, 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 were considered as comparators (para 5.4, maribavir PSD, November 2023 PBAC meeting).
- 7.5 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 investigator-assigned treatment (IAT, including ganciclovir or valganciclovir at standard or increased dose, or foscarnet or cidofovir). The PBAC recalled that it had previously considered that the 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 (para 7.10, maribavir PSD, November 2023 PBAC meeting). The PBAC noted that no additional trial data were presented in the resubmission.
- 7.6 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%)). The evaluation noted that pre-specified secondary outcomes of recurrence (during 8-week treatment, after 8-week treatment, and at any time during the study) were higher with maribavir than IAT (e.g., 56.5% vs 33.8% for recurrence at any time during the study). However, the resubmission argued that clinically relevant recurrence is better represented by recurrences after Week 8 (up to week 16) which required alternative anti-CMV treatment, occurring less frequently in maribavir patients than in IAT patients (26.0% vs 35.7%). The PBAC recalled it had previously considered that the claim of superior comparative effectiveness was not well-supported by the data (para 6.46, maribavir PSD, November 2023 PBAC meeting). The PBAC maintained that there was a high level of uncertainty in the magnitude of clinical benefit for maribavir due to the limitations of the trial but considered that the outcome of recurrence requiring retreatment was likely to be clinically meaningful and the SOLSTICE trial suggested maribavir was superior to IAT for this outcome.

- 7.7 The PBAC recalled it previously 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. The PBAC considered that the resubmission's claim of non-inferior safety was reasonable.
- 7.8 The PBAC recalled it previously considered there was a high level of uncertainty in the modelled outcomes because the economic evaluation was based on trial outcomes up to only 8 weeks and the model relied on multiple data sources and assumptions that were poorly justified (para 7.15, maribavir PSD, November 2023 PBAC meeting). The PBAC noted that the resubmission model still relied heavily on unjustified assumptions regarding subsequent treatment in patients without CMV viremia clearance, including those who did not achieve viremia clearance at week 8 and beyond and those who experience recurrence. The PBAC considered that the reduction in the duration of stage 1 of the model from 78 weeks to 39.2 weeks in the resubmission was appropriate and, to some extent, mitigates the impact of uncertainty from applying the short term observed data on clearance and mortality beyond the trial period. However, the model remained highly sensitive to the clearance effect of maribavir at week 8, which was uncertain due to the limitations of the trial.
- 7.9 The PBAC noted that the pre-PBAC response provided a revised base case which addressed some of the unjustified assumptions in the economic evaluation (treatment specific recurrence rates and IAT drug treatment durations) and proposed a price reduction for maribavir. The PBAC noted that this analysis resulted in an ICER of \$55,000 to < \$75,000 per QALY, however when the share of foscarnet retreatment was reduced by 50% and the time horizon shortened to 2 years the ICER increased to \$155,000 to < \$255,000 per QALY. The PBAC noted the advice provided in the sponsor hearing that response to maribavir is likely to be assessed frequently and use is likely to be similar to other treatments for CMV. Noting that the model assumed 7.5 weeks of maribavir treatment, and 5.14 weeks (average) for IAT, the PBAC considered that treatment costs for maribavir are likely to be overestimated in the model as they were driven by the 8-week trial design. The PBAC noted that the ICER was sensitive to the treatment duration for maribavir and when the duration was reduced to that of valganciclovir (5.64 weeks, the longest of IAT) the ICER was reduced from \$155,000 to < \$255,000 per QALY to \$5,000 to < \$15,000 per QALY. The PBAC considered that, although the treatment duration of maribavir in clinical practice is uncertain, the additional analysis provided reasonable assurance that maribavir would be cost effective at the price proposed in the pre-PBAC response.
- 7.10 The PBAC recalled it previously considered the submission's estimates that < 500 - < 500 patients per year would be treated with maribavir were reasonable and noted that these estimates were unchanged in the resubmission. The PBAC considered there remains uncertainty regarding both the length of treatment and the proportion of patients requiring retreatment. The PBAC considered that the treatment duration of 7.5 weeks was overestimated compared with SOLSTICE (6.91 weeks when compliance

was accounted for) and longer than maribavir is likely to be used in clinical practice. The PBAC considered the duration should be reduced to 5.64 weeks, consistent with consideration of treatment duration in the economic evaluation. The PBAC noted that when the treatment duration was reduced and the pre-PBAC proposed DPMQ for maribavir were applied, the total cost for maribavir was estimated to be \$0 to < \$10 million in Year 6, and a total of \$30 million to < \$40 million in the first 6 years of listing.

- 7.11 The PBAC considered that an RSA, with expenditure caps, would be required to mitigate the risk of a longer duration of treatment with maribavir, or frequent retreatment with maribavir, which would impact on the cost-effectiveness of maribavir. The PBAC considered that the financial estimates, with revisions as per paragraph 7.10, would be a reasonable basis for calculation of the expenditure caps.
- 7.12 The PBAC recommended that maribavir should not be treated as interchangeable on an individual patient basis with any other drugs.
- 7.13 The PBAC advised that maribavir is not suitable for prescribing by nurse practitioners.
- 7.14 The Early Supply Rule currently is not applied to some Section 100 Highly Specialised Drugs Program listings, including the antivirals: ganciclovir, valaciclovir and valganciclovir. The PBAC considered the Early Supply Rule should not apply to maribavir.
- 7.15 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for maribavir:
- a) The treatment is expected to provide a clinically relevant improvement in efficacy over alternative therapies, on the basis of CMV viraemia clearance however the magnitude of benefit is uncertain;
  - b) The treatment is not expected to address a high and urgent unmet clinical need as alternative treatments are available;
  - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 7.16 The PBAC noted that this submission is not eligible for an Independent Review as it is a positive recommendation.

**Outcome:**

Recommended

## **8 Recommended listing**

Add new item:

Public Summary Document - November 2024 PBAC Meeting

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
MARIBAVIR					
maribavir 200 mg tablet, 28	NEW	4	112	1	Liventicity
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>					
)	<b>Category / Program:</b> Section 100 – Highly Specialised Drugs Program {Public/Private/Community Access (CA)}				
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners				
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (Streamlined) [new digit code]				
	<b>Administrative Advice: Special Pricing Arrangements apply.</b>				
	<b>Administrative Advice: No increase in the maximum number of repeats may be authorised.</b>				
	<b>Condition: Cytomegalovirus (CMV) infection and disease</b>				
	<b>Indication: Cytomegalovirus (CMV) infection and disease</b>				
	<b>Clinical criteria:</b>				
	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/contraindicated to appropriately dosed ganciclovir, valganciclovir, cidofovir or foscarnet				
	OR				
	Patient must have received and is intolerant to continued use of appropriately dosed ganciclovir, valganciclovir, cidofovir or foscarnet.				
	<b>Prescribing instructions:</b>				
	Patients are determined to be refractory if after at least two weeks of appropriately dosed ganciclovir, valganciclovir, cidofovir or foscarnet, they fail to achieve a >1log <sub>10</sub> decrease in CMV DNA level.				
	Patients are determined to be resistant by the identification of a genetic alteration that decreases susceptibility to ganciclovir, valganciclovir, cidofovir or foscarnet.				
	Patients with Grade 3 neutropenia (absolute neutrophil count < 1000/mm <sup>3</sup> ) or impaired renal function (creatinine clearance < 50ml/min) are determined to be intolerant/contraindicated.				
	Maribavir should be used as monotherapy and use with valganciclovir or ganciclovir is contraindicated.				
	Maribavir should not be used in patients with demonstrated resistance to maribavir.				
	Maribavir should not be used in patients with CMV disease that involves the central nervous system.				
	Maribavir should not be used in patients with CMV retinitis.				

***These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.***

## 9 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.

## **10 Sponsor's Comment**

The sponsor had no comment.