maribavir film-coated tablets (Livtencity®)

Takeda UK Ltd

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

maribavir (Livtencity®) is accepted for use within NHSScotland.

Indication under review: treatment of cytomegalovirus (CMV) infection and/or disease that are refractory (with or without resistance) to one or more prior therapies, including ganciclovir, valganciclovir, cidofovir or foscarnet in adult patients who have undergone a haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT). Consideration should be given to official guidance on the appropriate use of antiviral agents.

In a phase III study, maribavir significantly improved confirmed CMV viraemia clearance at Week 8 compared with investigator-assigned therapy in patients with refractory CMV infection who had undergone HSCT or SOT.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Maribavir inhibits the UL97 protein kinase by competitively blocking ATP binding. This prevents the replication and maturation of cytomegalovirus (CMV) deoxyribonucleic acid (DNA), as well as its encapsidation and nuclear egress.[1] It is a first-in-class medicine for this indication.

The recommended dose of maribavir is 400mg orally twice daily for 8 weeks. Treatment duration may need to be individualised based on the clinical characteristics of each patient.[1]

1.2. Disease background

Human CMV (also known as human herpes virus 5) infection is widespread and can manifest as a mild, self-limiting illness in healthy individuals.[2] However, it poses a significant threat to patients with compromised immune systems, including solid organ transplant (SOT) and haematopoietic stem cell transplant (HSCT) recipients. In these transplanted patients, CMV can be reactivated or transmitted from donor tissue and can lead to serious CMV disease.[2] Uncontrolled CMV replication can lead to dissemination of the virus to multiple organs and result in end-organ diseases such as retinitis, colitis, oesophagitis, pneumonia, hepatitis, and meningoencephalitis. In addition, CMV infection is associated with indirect effects including opportunistic infections or graft-versus-host disease (GvHD) in HSCT recipients, or allograft loss in SOT recipients. Post-transplant CMV infection is also associated with substantial morbidity, a higher mortality risk, and increased cost of care.[2]

Despite CMV prevention strategies (prophylaxis or pre-emptive therapy), clinically significant CMV infection occurs in up to 35% of transplant patients. [2] Refractory CMV infection (persistence of CMV for ≥ two weeks despite treatment) occurring within the first 100 days after transplant is associated with an increased risk of CMV-induced organ disease and treatment-related mortality.[2]

1.3. Treatment pathway and relevant comparators

The management of post-transplant CMV infection primarily aims to prevent disease progression and complications during the period of profound immunosuppression by reducing CMV viraemia to undetectable levels. Once immune function recovers, antiviral protection against CMV is no longer needed.[2]

The current standard of care of post-transplant CMV disease or infection involves the empirical use of anti-CMV medicines such as ganciclovir, valganciclovir, foscarnet, and cidofovir. Apart from ganciclovir (indicated for the treatment of CMV disease in immunocompromised adults and adolescents ≥12 years of age), these are all used off-label.[3] Current treatments can have severe treatment-limiting toxicities (including bone marrow suppression with ganciclovir or valganciclovir, and renal impairment with foscarnet or cidofovir). Development of antiviral resistance to currently available anti-CMV agents, which can lead to graft loss and even death in some patients, is a clinical challenge in SOT and HSCT recipients.[2]

Clinical experts consulted by SMC (including hepatologists and haematologists) considered that, in the indication under review, foscarnet is the treatment most likely to be displaced by maribavir; while some of the experts noted that some use of ganciclovir and cidofovir may also potentially be reduced. However, depending on various factors the treatment used for each patient may vary.

Experts also suggested that valganciclovir is likely to remain as a first line treatment option for CMV infection and/or disease (before refractory status).

1.4. Category for decision-making process

Eligibility for a PACE meeting

Maribavir meets SMC orphan criteria.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of maribavir comes from SOLSTICE. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies

Criteria	SOLSTICE (SHP620-303)[2, 4-7]
Study design	Phase III, multicentre, randomised, open-label, active-controlled study
Eligible patients	The key inclusion criteria were: • Recipients of HSCT or SOT who were ≥12 years of age at the time of consent. • Documented CMV infection in whole blood or plasma, with a screening value of ≥2,730 IU/mL in whole blood or ≥910 IU/mL in plasma in two consecutive assessments, separated by at least 1 day, as determined by local or central specialty laboratory qPCR) or comparable quantitative CMV DNA results. Both samples should be taken within 14 days prior to randomisation, with second sample obtained within 5 days prior to randomisation. The same laboratory and same sample type (whole blood or plasma) must be used for these assessments. • Current CMV infection that is refractory to the most recently administered of the four anti-CMV treatment agents (ganciclovir, valganciclovir, foscarnet, or cidofovir). Refractory is defined as documented failure to achieve >1 $\log_{10}$ decrease in CMV DNA level in whole blood or plasma after a 14-day or longer treatment period with IV ganciclovir/oral valganciclovir, IV foscarnet, or IV cidofovir. Patients with documentation of one or more CMV genetic mutations associated with resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir must also meet the definition of refractory CMV infection.
Treatments	Maribavir 400mg twice daily or investigator-assigned (IAT) anti-CMV treatment for 8 weeks. Patients from the IAT group could be assessed for entry into a rescue arm after a minimum 3 weeks of treatment, for treatment with maribavir 400mg twice daily for 8 weeks, if they met the protocol-defined criteria.
Randomisation	Patients were randomised in a 2:1 allocation ratio according to two factors: • transplant type (HSCT or SOT) • most recent screening whole blood or plasma CMV DNA concentration categorised in to three CMV DNA concentration level groups based on local or central specialty laboratory qPCR results: - High viral load with CMV DNA ≥273,000 IU/mL in whole blood or ≥ 91,000 IU/mL in plasma, or - Intermediate viral load with CMV DNA ≥27,300 and <273,000 IU/mL in whole blood or ≥9,100 and <91,000 IU/mL in plasma, or - Low viral load with CMV DNA <27,300 and ≥2,730 IU/mL in whole blood or <9,100 and ≥910 IU/mL in plasma.

Primary outcome	Confirmed CMV viraemia clearance, defined as plasma CMV DNA concentrations below the LLOQ (that is <137 IU/mL) at the end of study Week 8. For clearance of CMV viraemia to be declared at the end of Study Week 8, the patient must have received exclusively study-assigned treatments.
Selected secondary outcomes	• Key secondary outcome: composite of confirmed CMV viraemia clearance and symptom control at the end of Week 8, maintained through Week 16 (8 weeks beyond treatment phase) after receiving exclusively study-assigned treatment. Symptom control was defined as resolution/improvement of CMV disease/syndrome for patients symptomatic at baseline; or absence of the development of CMV disease/syndrome for patients asymptomatic at baseline. CMV disease/syndrome was assessed by the investigator; assessments were adjudicated by an independent, blinded Endpoint Adjudication Committee. • Recurrence of CMV viraemia (plasma CMV DNA concentration greater than or equal to the LLOQ when assessed by the central laboratory in two consecutive plasma samples at least 5 days apart, after achieving confirmed viraemia clearance) during the first 8 weeks of the study, in the follow-up period of 12 weeks, and at any time during the 20 weeks of the study, regardless of whether either study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy. • All-cause mortality.
Statistical analysis	Efficacy analyses were performed in the randomised population, which included all patients who underwent randomisation. Subjects were to be analysed in the treatment group to which they are randomised. To control the family-wise Type 1 error rate at 5% level, a hierarchical statistical testing strategy was applied in the study for the primary (tested first) and key secondary endpoint (tested second) with no formal testing of outcomes after the first non-significant outcome in the hierarchy.
CMV = cytomegalovirus; DNA = Deoxyribonucleic acid; HSCT = haematopoietic stem cell transplant; IU = international units; IV = intravenous; LLOQ = lower limit of quantification; qPCR = quantitative polymerase chain reaction; SOT = solid organ transplant	

A significantly higher proportion of patients in the maribavir group achieved confirmed CMV viraemia clearance at Week 8 compared with the IAT group. Results for the primary and selected secondary outcomes are detailed in Table 2.2.

Table 2.2. Primary and selected secondary outcomes of SOLSTICE[2, 4-7]

	Maribavir 400mg twice daily (N=235)	**IAT (N=117)**	**Adjusted difference in percentage of responders (95% CIs)**
Primary outcome			
CMV viraemia clearance at end of Week 8, %	56%	24%	33% (23% to 43%) p< 0.001
Selected secondary outcomes			
Composite of confirmed CMV viraemia clearance and symptom control at the end of Week 8, maintained through Week 16, %	19%	10%	9.5% (2.0% to 17%) p<0.05

Recurrence[a] of CMV viraemia during the first 8 weeks of the study, %	18% (33/184)	12% (8/65)	-
Recurrence[a] of CMV viraemia in the 12-week follow-up period, %	39% (71/184)	22% (14/65)	-
Recurrence[a] of CMV viraemia at any time during the 20-week study, %	57% (104/184)	34% (22/65)	-
All-cause mortality, %	11%	11%	-
CI= confidence interval; CMV= cytomegalovirus; IAT= investigator-assigned therapy; LLOQ= lower limit of quantification [a]in patients who had CMV viraemia clearance after study assigned at any time on study			

Twenty-two patients from the IAT group entered the maribavir rescue arm based on the protocol-defined criteria. Of these, 50% (11/22) of patients achieved confirmed CMV viraemia clearance at Week 8 of the maribavir rescue treatment phase. [2]

2.2. Health-related quality of life outcomes

Health-Related Quality of Life (HRQoL) was assessed using the European Quality of Life 5-Dimension 5-Level (EQ-5D-5L) and Short Form-36 version 2 (SF-36v2) instruments. However, no clear conclusions can be drawn from results.[7]

2.3. Supportive study

The submitting company provided data from TAK620-5004, a retrospective study collecting follow-up data at 12 months from patients randomised to the maribavir arm in the SOLSTICE study. Among the 109 patients enrolled in this study, 16% died during the full study period (that is from randomisation through Week 52), including three SOT patients and 14 HSCT patients.[8, 9]

3. Summary of Safety Evidence

Overall, the safety profile of maribavir was considered more favourable, when compared with the currently available anti-CMV therapies, and manageable in the treatment context, with dysgeusia and abdominal complaints as the main side effects.[2]

In the SOLSTICE study, the median duration of exposure in the maribavir group was 57 days and in the IAT group was 34 days. Any treatment-emergent adverse event (AE) was reported by 97% (228/234) of patients in the maribavir group and 91% (106/116) in the IAT group and these were considered treatment-related in 60% and 49% respectively. In the maribavir and IAT groups respectively, patients reporting a severe AE (defined as an adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention) were 32% versus 38% and it was considered treatment related in 3.8% and 21% of patients; patients with a reported serious AE were 39% versus 37% (treatment related in 5.1% and 15%); patients with a treatment discontinuation due to treatment emergent AEs were 13% versus 32% (treatment related in 4.7% and 23%); the proportion of AEs that led to study discontinuation were 7.3% versus 7.8% (treatment related in 1.3% and 1.7%).[4]

The most frequently reported treatment-related AEs (>5%) of any grade in the maribavir group versus the IAT group were: dysgeusia (36% versus 0.9%), nausea (8.5% versus 9.5%), taste disorder (8.5% versus 0.9%), neutropaenia (1.7% versus 14%), vomiting (7.7% versus 4.3%), anaemia (1.3 % versus 7.8%), acute kidney injury (1.7% versus 7.8 %), immunosuppressant drug level increased

(6.0% versus 0), thrombocytopenia (0 versus 5.2%) and diarrhoea (3.8% versus 5.2%). [4] Of note, the summary of product characteristics (SPC) states that the plasma levels of immunosuppressants must be frequently monitored throughout treatment with maribavir, especially following initiation and after discontinuation of maribavir, and doses should be adjusted, as needed.[1]

Any serious AE with an outcome of death occurred in 6.8% and 5.2% of patients; it was deemed to be treatment related by the investigator in one patient in each group..[4]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In the SOLSTICE study, maribavir significantly improved CMV viraemia clearance compared with other treatments in patients with refractory CMV infection who had undergone HSCT or SOT. The antiviral activity of maribavir, as demonstrated by the objective and validated key study primary outcome, was considered clinically relevant.
- Regulators concluded that maribavir could be a useful treatment option for patients that do not achieve virological control with first-line agents such as ganciclovir.[2]
- The safety profile of maribavir was considered more favourable than currently available anti-CMV treatments (with no evident haematological or renal toxicity unlike some of the other anti-CMV treatment options).

4.2. Key uncertainties

- The open-label design of the key study and several post-randomisation changes made to the protocol may have introduced bias, potentially placing the IAT group at a disadvantage over the maribavir group. Despite these concerns, the data were regarded by regulators as sufficiently robust for decision-making purposes.[2]
- Within the 8-week treatment period, treatment discontinuations were much higher with IAT (68%) than with maribavir (22%). Regulators noted concerns that in some countries patients may have been required to pay for IAT but not maribavir. This could have impacted the results in the IAT group and could potentially explain the high rate of failures other than lack of virological clearance in the IAT group. Despite these concerns, regulators considered there was no indication of bias sufficient to question the overall positive study results. [2]
- There is uncertainty about whether the proportion of patients treated with each option in the comparator arm (including foscarnet [40%], ganciclovir [24%] and valganciclovir [24%]) is reflective of what would be used in practice in Scotland; and the response rate observed in the IAT group was described by regulators as lower than that observed in clinical practice. In addition, response rate in the IAT group could have been influenced by the high rate of patients being resistant to their assigned IAT (57% [32/56] of patients identified as having one or more baseline resistance-associated amino acid substitution (RASs) known to confer resistance to ganciclovir/valganciclovir received ganciclovir/valganciclovir as the IAT).[2]
- The majority of patients in the study had asymptomatic CMV infection at baseline (86%).[2] This may limit the generalisability of the results to patients with CMV disease. During the study,

more recurrences of CMV viraemia were seen in maribavir-treated patients that in IAT-treated patients (especially after cessation of therapy). This was considered to be in line with the key secondary outcome data, indicating that sustainability of viraemia clearance and symptom control is not substantial with maribavir treatment, compatible with a low barrier to resistance. A cautionary statement to inform the prescriber that virologic failure can occur during and after treatment with maribavir was included in the SPC.[2]

- There are no comparative data beyond Week 20 and no statistically significant effect on mortality was able to be observed in the SOLSTICE trial.
- Based on subgroup analysis, it appears that maribavir benefit may be lower in terms of viraemia clearance in the refractory population with no prior treatment resistance.

4.3. Clinical expert input

Clinical experts consulted by SMC advised that maribavir fills an unmet need in this therapeutic area and is a therapeutic advancement, as it is an effective treatment option that is administered orally and has fewer toxicities than alternative treatment options.

4.4. Service implications

Maribavir offers an orally administered treatment option, which may be preferable to patients over current parenterally administered anti-CMV treatments and may lead to beneficial impacts on service delivery.

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Groups.

- We received a joint patient group submission from Anthony Nolan and Leukaemia Care, which are both registered charities.
- Anthony Nolan has received 6% pharmaceutical company funding in the past two years, including from the submitting company. Leukaemia Care has received 27% pharmaceutical company funding in the past two years, including from the submitting company.
- Refractory or resistant post-transplant CMV infections have serious effects on a patient's quality of life, can delay their post-transplant recovery and result in extended in-patient stays. The experience of refractory or resistant post-transplant CMV infection, and the associated effects, can also have a significant psychological impact for patients and their families. There are also financial consequences with some patients having to abandon work commitments resulting in the partner and other family members bearing the entire financial burden and responsibility of supporting the family.
- All current treatments have toxicity and severe side effects, which significantly impact upon patients' daily life and independence. Intravenous treatments mean that patients are required to spend time in hospital, either on a day basis or as an in-patient. This had a significant effect on patients' ability to have a normal life, including working and having a social life.

- Patients generally favour a treatment that can be administered orally. Maribavir, as an oral therapy, is therefore likely to improve a patient's experience of treatment and quality of life, due to its convenience and the option to take it at home. It is also hoped it may provide a more tolerable alternative to currently available medicines.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case, as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	47 years.
Population	The submitting company requested SMC consider maribavir for the full indication: treatment of CMV infection and/or disease that are refractory (with or without resistance) to one or more prior therapies, including ganciclovir, valganciclovir, cidofovir or foscarnet in adult patients who have undergone an HSCT or SOT.
Comparators	Investigator-assigned anti-CMV treatment (IAT). This was comprised of ganciclovir (25%), valganciclovir (26%), foscarnet (44%), and cidofovir (5%).
Model description	The model was a two-stage Markov model. The duration of stage 1 was 39.2 weeks. The stage 1 model had three health states, clinically significant CMV (csCMV), non-clinically significant CMV (n-csCMV) and dead. All patients entered the model in the csCMV health state and were initially treated with maribavir or IAT depending on the treatment arm. After completion of initial treatment at week 8, patients could transition to the n-csCMV health state according to week 8 clearance probabilities; otherwise, they would remain in the csCMV health state to receive IAT retreatment. In the n-csCMV health state, patients could experience a clinically significant recurrence and return to the csCMV health state to receive IAT retreatment. The probability of recurrence decreased the longer the time spent in the n-csCMV health state. Patients retreated with IAT could be cleared and transition to the n-csCMV health state. In stage 1, all patients could transition to a self-absorbing death state. Disease complications of graft loss and GvHD were also included in the stage 1 model. All patients alive at the end of stage 1, transitioned to the two state alive/dead model of stage 2. Within the stage 2 Markov model, all patients in the alive state could transition to death according to transplant specific (SOT or HSCT) mortality. The model used a 4-week cycle length for the first 3 years, switching to annual cycles after. A half-cycle correction was applied from week 12 onwards. The half cycle correction was not included before week 12 to preserve the observations of the trial data in the first 8 weeks.
Clinical data	SOLSTICE was the primary source of clinical data informing the treatment effectiveness in the model for maribavir. In addition to SOLSTICE, the submitting company also utilised data from OTUS (outcomes, treatment patterns and healthcare resource utilisation studies). OTUS data were used to estimate the clearance probability for IAT therapy at 8 weeks, to which an unadjusted odds ratio of clearance (comparing maribavir to IAT) from SOLSTICE was applied to estimate the week 8 maribavir clearance probability. Later clearance probabilities in Stage 1 of the model were derived from the SOLSTICE IAT arm for both arms week 8 onwards, applied as 4 weekly). Probabilities of recurrence were derived from OTUS data. The IAT distribution was from SOLSTICE.
Extrapolation	In stage 1 of the model, extrapolation was present in the post-week 8 clearance probabilities in the maribavir and IAT arms, as the submitting company assumed these would be equal to the derived week 8 IAT clearance probability from SOLSTICE. Stage 1 utilised mortality data from OTUS and applied relative risks from published literature. [10, 11] In stage 2 of the model, published literature for SOT[12] and HSCT mortality[13] were used.

Quality of life	Utility values used in the model for the csCMV and n-csCMV health states in stage 1 were derived from SOLSTICE EQ-5D-5L. In stage 2 of the model a disutility between the week 20 SOLSTICE utility values and the general UK population at 53 years (model starting age) was calculated, with this then applied to the mean UK population utility values in every model cycle. Dis-utilities for graft loss, GvHD and adverse events were also included in the model.
Costs and resource use	The model included medicine acquisition, administration, and monitoring costs. Other costs included in the model were csCMV and n-csCMV health resource utilisation (hospitalisation), graft loss, GvHD, and adverse events. Separate time on treatment for both maribavir and IAT were obtained from SOLSTICE and were applied as initial treatment and retreatment durations. csCMV and n-csCMV health resource utilisation (hospitalisation) probabilities were derived from SOLSTICE. Monitoring frequencies were estimated from product SPCs.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

6.2. Results

The base case results indicated that maribavir was dominant compared to IAT, meaning it was estimated as resulting in lower costs and better health outcomes for patients. The majority of total costs in the maribavir arm were from the acquisition of maribavir. There were incremental cost savings for retreatment, health resource utilisation, administration and adverse events in the maribavir arm. The incremental QALY gain for maribavir was obtained primarily through increased time in the n-csCMV health state and a greater accrual of QALYs for survival in stage 2 of the Markov model.

Table 6.2: Base case results with PAS

	ICER incremental (£/QALY)
Maribavir versus IAT	Maribavir dominant (-£4,133)
ICER: Incremental cost-effectiveness ratio; PAS: Patient access scheme; QALY: Quality-adjusted life year; IAT: Investigator-assigned anti-CMV treatment; Dominant: The assessed medicine was estimated as having lower costs and greater health outcomes than the comparator.	

6.3. Sensitivity analyses

Key scenario analyses are shown in Table 6.3 (inclusive of maribavir PAS). The largest changes were observed when using only foscarnet for treatment and retreatment, removing the stage 1 mortality advantage in n-csCMV, and excluding retreatment costs.

Table 6.3: Scenario analysis results (with PAS)

	Description	**Base case**	**Scenario**	**ICER (£/QALY)**
1	Base case	--	--	-£4,133 (maribavir dominant)
2	Comparator	IAT	Foscarnet only	-£32,350 (maribavir dominant)
3	Recurrence transition probabilities	OTUS	SOLSTICE (pooled recurrence*) and OTUS	-£3,080 (maribavir dominant)
4	Stage 1 to stage 2 transition	39.2 weeks	52 weeks	-£7,376 (maribavir dominant)
5a	IAT clearance week 8	Base case value	Decrease by 20%	-£7,109 (maribavir dominant)

	Description	Base case	Scenario	ICER (£/QALY)
5b	IAT clearance week 8	Base case value	Increase by 20%	£427
6a	Maribavir clearance week 8	Base case value	Decrease by 20%	£7,676
6b	Maribavir clearance week 8	Base case value	Increase by 20%	-£9,078 (maribavir dominant)
7	Stage 1 mortality	Reduced mortality for n-csCMV	Mortality advantage removed	-£103,014 (maribavir dominant)
8	Time Horizon	47 years	1 year	-£37,245 (maribavir dominant)
9	IAT distribution	SOLSTICE	OTUS (investigator defined)	£7,883
10	Retreatment costs	Included	Excluded	£9,978

ICER: Incremental cost-effectiveness ratio; PAS: Patient access scheme; QALY: Quality-adjusted life year; IAT: Investigator-assigned anti-CMV treatment; OTUS: Outcomes, treatment patterns and healthcare resource utilisation studies. *Recurrence from the pooled SOLSTICE trial population (maribavir and IAT arms) who achieved clearance, measured over the remaining 12 weeks of the SOLSTICE trial; Dominant: The assessed medicine was estimated as having lower costs and greater health outcomes than the comparator.

6.4. Key strengths

- The model structure captured the key health states associated with CMV with assumptions validated by SMC clinical experts.
- The data from OTUS complemented SOLSTICE, providing evidence for standard of care outcomes beyond the 20-week trial period.
- The company conducted a vignette study to derive additional appropriate health-related utility data, supporting the utility estimates from SOLSTICE.

6.5. Key uncertainties

- The increased mortality rates for csCMV in stage 1 of the model were a source of uncertainty. Although the submitting company provided analysis showing a separation of maribavir and IAT mortality curves in SOLSTICE post-week-8, SOLSTICE did not show a significant difference between mortality in the two treatment arms. Therefore, the magnitude of csCMV mortality and associated QALY benefit for maribavir were uncertain. In a conservative scenario, the mortality advantage was removed for csCMV. Although this reduced the QALY gain, as maribavir still demonstrated cost savings it remained dominant (Scenario 7).
- The cost of IAT was potentially overestimated as there may be patients within the model cohort receiving ongoing IAT retreatment for several cycles until the transition to stage 2 of the model. In a conservative scenario, excluding retreatment costs from the model resulted in an ICER of £9,978 (Scenario 10). The limitation of this analysis was that no clinical data

adjustments were made and only costs were affected. In sum, although uncertainty in IAT costs was identified, the scenario ICER was likely conservative and expected to be lower.

- The submitting company used data from two real world studies (OTUS) to provide estimates of longer-term outcomes in the economic model. Although this was likely beneficial to supplement SOLSTICE data that were only collected for 20 weeks, it created uncertainty as there was an assumption that the populations of these studies were interchangeable. Sensitivity analysis, including on clearance and recurrence probabilities (Scenarios 3, 5 and 6), and the IAT distribution (Scenario 9), provided indicative evidence that substantive ICER increases would be unlikely.

*Other data were also assessed but remain confidential.**

7. Conclusion

After considering all the available evidence, the Committee accepted maribavir for use in NHSScotland.

8. Guidelines and Protocols

Relevant guidelines include:

- UK guideline on prevention and management of cytomegalovirus (CMV) infection and disease following solid organ transplantation. British Transplantation Society. 2023[14]
- Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7). 2019[15]
- The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation. The Transplantation Society International CMV Consensus Group. 2018[16]

9. Additional Information

9.1. Product availability date

Available.

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per course (£)
maribavir	**daily dose of 800mg for 8 weeks**	**£46,200**

Costs from BNF online on 05/07/2023. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 11 August 2023.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.