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CADTH Reimbursement Recommendation

Maribavir (Livtencity)

Indication: Treatment of adults with post-transplant cytomegalovirus infection/disease who are refractory (with or without genotypic resistance) to 1 or more prior antiviral therapies.

Sponsor: Takeda Canada Inc.

Final recommendation: Reimburse with conditions

CADTH

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Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Livtencity?

CADTH recommends that Livtencity should be reimbursed by public drug plans for the treatment of adults with post-transplant cytomegalovirus (CMV) infection/disease who are refractory (with or without genotypic resistance) to 1 or more prior antiviral therapies if certain conditions are met.

Which Patients Are Eligible for Coverage?

Livtencity should only be covered to treat adult patients with CMV infections that are refractory (with or without resistance) to 1 or more of the following antiviral drugs: valganciclovir, ganciclovir, foscarnet, or cidofovir.

What Are the Conditions for Reimbursement?

Livtencity should only be reimbursed if prescribed by clinicians with experience and expertise in transplant medicine, transplant infectious disease, or infectious diseases, and if the cost of Livtencity is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that in patients with refractory CMV infection, with or without resistance to antiviral drugs, treatment with Livtencity cleared the virus from the bloodstream in more patients than other antivirals. Treatment with Livtencity also resulted in maintaining virus clearance and symptom control.
- Livtencity meets some of the needs identified by patients, namely a more effective treatment option for controlling the infection and symptoms.
- Based on CADTH's assessment of the health economic evidence, Livtencity does not represent good value to the health care system at the public list price; thus, a price reduction is required.
- Based on public list prices, Livtencity is estimated to cost the public drug plans approximately $30 million over the next 3 years.

Additional Information

What Is CMV Infection?

CMV infection is a common infection caused by a type of herpes virus. Most people do not experience symptoms; however, it can cause serious complications in patients with weakened immune systems, such as transplant recipients. Serious complications include disease of the infected organ (e.g., liver, lung, digestive tract) or rejection of the transplanted organ. The prevalence of post-transplant CMV infection in Canada is unknown. Estimates of refractory CMV infection in Europe and the US are between 19% and 21% for recipients of solid organ transplant (SOC) and 9% and 47% for recipients of hematopoietic stem cell transplant (HSCT).

Unmet Needs in CMV Infection

Currently available antiviral treatments are often associated with severe side effects, and there are limited options when treatments are ineffective (i.e., refractory infection) or the infection becomes resistant to available antiviral drugs.

How Much Does Livtencity Cost?

Treatment with Livtencity is expected to cost approximately $58,128 per patient per 7.5-week course of treatment.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that maribavir be reimbursed for the treatment of adults with post-transplant CMV infection/disease who are refractory (with or without genotypic resistance) to 1 or more prior antiviral therapies only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One open-label, randomized, double-arm, phase III trial (SOLSTICE, N = 352) demonstrated that treatment with maribavir resulted in greater achievement of CMV viremia clearance, as well as maintenance of viremia clearance and symptom control compared to investigator-assigned anti-CMV treatment (IAT) in recipients of SOT or HSCT who had refractory CMV infection with or without resistance. Evidence from the SOLSTICE trial demonstrated that, compared with IAT (monotherapy or dual-combination of IV ganciclovir, oral valganciclovir, IV foscarnet, or IV cidofovir), 8 weeks of treatment with maribavir was associated with statistically significant and clinically meaningful improvement in confirmed CMV viremia clearance at the end of week 8 (55.7% versus 23.9%; 32.8% adjusted difference; 95% confidence interval [CI], 22.80 to 42.74; P < 0.001). Treatment with maribavir, compared to IAT, was also associated with greater confirmed CMV viremia clearance and symptom control at the end of week 8 and maintained through week 16 (8 weeks beyond the treatment phase; 18.7% versus 10.3%; 9.5% adjusted difference; 95% CI, 2.02% to 16.88%; P = 0.013).

Patients identified the need for effective treatments that improve outcomes, reduce mortality, relieve symptoms, have fewer or less severe side effects, improve health-related quality of life (HRQoL), and eliminate admission to the hospital. CDEC concluded that treatment with maribavir meets some of these needs as numerically fewer patients treated with maribavir in the SOLSTICE study discontinued treatment due to adverse events (AEs) compared to IAT. Furthermore, lower rates of hematologic and renal toxicities observed with maribavir treatment may fill a gap in the treatment landscape whereby other drugs have known toxicities that limit their use; however, the potential comparative safety benefit of maribavir is not known. Patients identified a need for more treatment options that are easy to administer; the oral formulation of maribavir meets this need.

Using the sponsor-submitted price for maribavir and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio for maribavir was $403,089 per quality-adjusted life-year (QALY) compared with IAT (combined comparator of ganciclovir, valganciclovir, foscarnet, and cidofovir). At this the incremental cost-effectiveness ratio, maribavir is not cost-effective at a $50,000 per QALY willingness-to-pay threshold for adult recipients of SOT or HSCT who have CMV infection/disease that is refractory (with or without genotypic resistance) to 1 or more prior antiviral therapies. A price reduction is required for maribavir to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with maribavir should only be reimbursed when initiated in adult patients with CMV infections that are refractory (with or without resistance) to 1 or more of the following antiviral drugs: valganciclovir, ganciclovir, foscarnet, or cidofovir.	Evidence from the SOLSTICE trial demonstrated that maribavir resulted in a statistically and clinically significant improvement in viremia clearance and symptom control in patients who had previously been treated with antiviral drugs. The antiviral drugs listed in condition 1 are used to treat CMV in Canada.	CMV infection that is refractory (with or without resistance) is defined as a lack of change in CMV viral load or increase in CMV viral load after at least 2 weeks of appropriately dosed treatment.
Renewal		
2. Subsequent treatment with maribavir may be reimbursed for patients who have a recurrence of CMV viremia after a previous successful course of therapy with maribavir.	According to the clinical experts, if a patient requires re-treatment due to CMV recurrence, it is likely that they would be re-treated with the initial treatment used (i.e., patients who received maribavir would be re-treated with maribavir). If patients are non-responders, the clinical experts noted that they would be treated by a different antiviral drug.	—
Discontinuation		
3. Maribavir must be discontinued in patients with 1 of the following: 3.1. no change or an increase in CMV viral load after at least 2 weeks of maribavir treatment 3.2. confirmed CMV genetic mutation associated with resistance to maribavir.	Based on clinical expert input, these conditions represent standard of care in Canada for discontinuing treatment of antiviral drugs in this patient population. The clinical experts noted that treatment duration is variable and is individualized based on multiple patient characteristics (e.g., GVHD, toxicity).	—
Prescribing		
4. Maribavir should be prescribed by clinicians with experience and expertise in transplant medicine, transplant infectious disease, or infectious diseases.	To ensure that maribavir is prescribed only for appropriate patients and adverse events are managed in an optimized and timely manner.	—
Pricing		
5. A reduction in price	The ICER for maribavir is $403,089 when compared with IAT. A price reduction of at least 4.5% would be required for maribavir to be able to achieve an ICER of $50,000 per QALY compared to IAT.	—

CMV = cytomegalovirus; GVHD = graft-versus-host disease; IAT = investigator-assigned treatment; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Discussion Points

- CDEC acknowledged that there is a need for an effective treatment for patients with post-transplant CMV infection/disease that is refractory (with or without resistance) to prior antiviral therapies. Current treatments for CMV infection are not effective in clearing CMV viremia in all patients, are associated with severe adverse effects or the development of resistance, and may require that the patient travel to a hospital or clinic for administration.
- CDEC deliberated on the results from the SOLSTICE study that suggested that maribavir is more efficacious compared to IATs (currently available therapies) in achieving CMV viremia clearance and symptom control. However, CDEC discussed that no conclusion can be reached regarding the effects of maribavir on some of the outcomes sought by patients, such as mortality, CMV recurrence, HRQoL, and hospital stays. Also, the potential comparative safety benefit of maribavir is not known.
- CDEC acknowledged that there is uncertainty in the generalizability of the evidence from the SOLSTICE trial, in particular pertaining to duration and place in therapy of maribavir. In clinical practice in Canada, the treatment duration of maribavir may vary considerably. Furthermore, although the comparators used in the trial are reflective of clinical practice, the distribution or frequency of use of selected antiviral therapies was described by the clinical experts as being inconsistent with Canadian clinical practice. There is also uncertainty in the benefit of maribavir when administered in combination with other antivirals and on the impact of treatment-emergent resistance.
- CDEC acknowledged the uncertainty in the cost-effectiveness of maribavir, where lengthened treatment durations beyond 8 weeks may negatively impact cost-effectiveness. Further, the extent of savings in using maribavir to avert drug administration costs with IV drugs are uncertain, especially if maribavir is not being administered in an outpatient setting. Given the absence of comparative effectiveness to each antiviral drug grouped with IAT versus maribavir, which clinical experts considered nonrepresentative of use in Canadian practice, any cost-effectiveness estimate is highly uncertain.

Background

Maribavir (Livtencity) is an oral tablet indicated for the treatment of adults with post-transplant CMV infection/disease who are refractory (with or without genotypic resistance) to 1 or more prior antiviral therapies. The Health Canada–recommended dose is 400 mg (two 200 mg tablets) twice daily, resulting in a daily dose of 800 mg.

The number of patients undergoing transplants in Canada has been rising over the past decades. The Canadian Institute for Health Information reported that the number of SOT procedures in Canada (excluding Quebec) increased from 1,036 in 2011 to 2,594 in 2020. Similarly, the Canadian Institute for Health Information reported that the number of autologous and allogeneic HSCT procedures in Canada increased steadily from 1,236 in 2010 to 1,605 in 2014. Despite the limited data on refractory and resistant CMV infections in the Canadian context, the sponsor-submitted systematic review found that between 19% and 21% of those receiving SOT and 9% and 47% of those receiving HSCT experienced refractory CMV infection in Europe and the US. The majority of studies (4 studies) identified in the sponsor's systematic review reported resistant CMV infection in 1% to 8% of recipients of SOT, with 1 study from the Netherlands reporting that as many as 37% of recipients of

SOT had mutations conferring CMV resistance. In patients receiving HSCT, 2% to 3% had resistant infection.

CMV is a beta-herpes virus that remains dormant in the human body for life after primary infection. Patients with compromised immune systems, immune suppression in preparation for transplant, and post-transplant maintenance immunosuppression are at significantly increased risk of CMV infection, which can manifest into clinical complications, including CMV disease. CMV infection may be asymptomatic and only detectable by viral replication; however, when symptoms are present (i.e., in the case of CMV infection manifesting into CMV disease or CMV syndrome) patients may experience fever, low white blood cell counts (leukopenia), muscle weakness, fatigue, shortness of breath, blurry vision or loss of vision, abdominal pain, blood in stools, nausea, vomiting, or diarrhea. The possible complications of CMV in patients who received transplant include transplant failure, liver and digestive disease (e.g., hepatitis or colitis) and infections in different organs (e.g., pneumonia, pancreatitis, meningitis, myocarditis) or the blood.

The most widely used antivirals for first-line preemptive therapy are IV ganciclovir, oral valganciclovir, and IV foscarnet. When patients are resistant to available treatment, subsequent therapy options are limited. No treatments are currently approved by Health Canada for patients with refractory or resistant CMV.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III, multicentre, open-label, randomized controlled trial (SOLSTICE)
- patient perspectives gathered by 9 patient groups: the Kidney Foundation of Canada, the Canadian Liver Foundation, the Leukemia and Lymphoma Society of Canada, Myeloma Canada, the Aplastic Anemia and Myelodysplasia Association of Canada, Lymphoma Canada, the Myeloproliferative Neoplasm Canadian Research Foundation, the Canadian Myeloproliferative Neoplasm Network, the Canadian Chronic Myelogenous Leukemia Network, and Chronic Lymphocytic Leukemia Canada
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with of post-transplant CMV infection and/or disease in adults
- input from 1 clinician group, Cell Therapy Transplant Canada (CTTC)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

A total of 9 patient advocacy groups provided input on maribavir for the treatment of adults with post-transplant CMV infection/disease that is refractory and/or resistant to 1 or more

prior antiviral therapies. The groups conducted a total of 3 surveys to capture input. The patients were predominantly those with myeloma and/or autologous HSCT, noted by clinical experts to be a group for which CMV infection is not a concern, rather than patients who are recipients of allogenic HSCT and are at risk for CMV infection. Patients reported on the negative impact of staying in the hospital and away from home for weeks to months for treatment. CMV infection also affected patients' ability to work and perform in school, mental health (i.e., stress and anxiety), ability to care for and spend time with families and friends, sexual life (i.e., intimacy concerns due to spreading CMV to their partners), and finances. Patients value effective medications with fewer side effects (e.g., taste disturbances, nausea, vomiting, feeling weak or tired, urinary changes), no contraindications and interactions with immunosuppressants, that are simple to administer, and that are covered by the drug plans. Patients also value an improvement to their quality of life, relieving CMV infection, eliminating overnight stays at a hospital, and reducing the severity of side effects (most commonly anxiety; weight loss; pain in the back, joints, or muscles; and diarrhea) caused by currently available treatments. Availability of maribavir may allow patients to be treated closer to home and potentially have an impact on improving equity or access to treatment.

Clinician Input

Input From the Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH identified that, based on the limitations of existing therapies, the goals of anti-CMV treatment are to control the virus and its symptoms until a patient's immune system is strong enough to fight the virus (rather than eradicating it). As such, the goals of existing treatments are to improve symptoms (if the patient has end-organ disease), reduce mortality, improve graft function and/or reduce graft loss, minimize adverse effects, and improve quality of life.

The clinical experts indicated that challenges with existing treatments include high rates of hospitalizations for treatment administration and toxic side effects. The clinical experts also described concerns around patients becoming resistant to current treatment options, though they likely expect patients using maribavir to develop resistance, as well. The clinical experts stressed the importance of treating patients with the least toxic and most effective drug early, citing that some of the outcomes from delayed treatment are irreversible (e.g., graft loss due to ganciclovir or valganciclovir that causes myelosuppression that cannot be reversed).

According to the clinical experts, definitions of resistance and refractory are important to identify patients most suitable for treatment with maribavir. Patients most likely to respond to maribavir include those who have intolerances or life-threatening side effects to other drugs, those who can have their immunosuppression reduced, and/or those who can have their immune function improve.

In routine clinical practice, the clinical experts indicated that anti-CMV treatment is given until CMV is either negative or "low level"; however, the definition of "low level" is unclear and treatment duration must be individualized based on multiple patient characteristics; for example, graft-versus-host disease (GVHD) or toxicity.

Per the clinical experts, complete response to maribavir would be defined as resolution of symptoms of end-organ disease and eradication of CMV viremia.

Clinician Group Input

CADTH received input from 1 clinician group, CTTC.

The input provided by CTTC generally aligned with the input provided by the clinical experts consulted by CADTH. Pertaining to the patient population, the clinician group added that patients who are post-transplant often struggle with a lack of appetite and/or poor oral intake; therefore, the patients with eating difficulties might be less suitable for maribavir, which is associated with dysgeusia/ However, the clinician group emphasized that the toxicity profile of conventional salvage therapies is much more concerning. Furthermore, the group emphasized that it is particularly challenging to treat CMV infection in patients with GVHD because GVHD therapies are immunosuppressive (i.e., increase the risk of CMV infection), myelosuppressive (i.e., exacerbate the toxicities caused by valganciclovir), and nephrotoxic (i.e., exacerbate the toxicities caused by foscarnet).

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Considerations for initiation of therapy	
What is the definition of refractory and resistant CMV in clinical practice? What parameters are used?	According to the clinical experts, refractory CMV in trials is a 1-log10 rise in CMV viral load after 2 weeks of appropriately dosed antiviral therapy, probable refractory CMV is a CMV viral load that does not decrease in the same time frame, and resistant CMV refers to the viral genotyping that has mutations associated with reduced response to antiviral therapy. CDEC agreed with the clinical experts who expressed that, in routine clinical practice, viral load may not be reported in log numbers; therefore, stable or rising CMV viral loads on the week 3 viral load assessment despite appropriate therapy are usually taken as an indication of refractory or resistant CMV. Clinicians are concerned with any numerical rise in CMV viral loads but sometimes these do not fit the log definition and if testing is repeated too frequently or early, viral loads can fluctuate as much of the CMV in plasma is fragmented and does not represent whole genomes. The experts added that resistance testing is normally administered in this setting.
Will prior antiviral therapies be limited to ganciclovir, valganciclovir, foscarnet, and cidofovir? Would it also include letermovir (Prevymis)?	CDEC agreed with the clinical experts that prior antiviral therapies typically include ganciclovir and/or valganciclovir or foscarnet, unless there are extenuating circumstances. In SOT, ganciclovir and/or valganciclovir are the first-line therapies, per the experts. In certain cases, cidofovir may be used; however, the experts indicated that it is a weak antiviral with renal and ocular toxicity. The experts also highlighted that resistance to ganciclovir in the *UL54* gene often comes with cidofovir resistance, so the drug may be ineffective. According to the clinical experts, letermovir is generally not included in prior antiviral therapies as it only has case-report level data on use as treatment for refractory or resistant CMV and appropriate dosing levels for routine clinical practice have not been identified.

Implementation issues	Response
Can maribavir be used in combination with other antivirals used for CMV prevention and treatment in transplant recipients?	CDEC agreed with the clinical experts that maribavir has failed in trials of prevention in the HSCT population so it should not be used for this purpose. To treat CMV, the clinical experts noted that maribavir could possibly be used in combination therapy with foscarnet for patients who may be at risk of failing on maribavir alone (e.g., patients with very high viral loads at the time of therapy initiation); however, there are no data on how best to do this (i.e., which patient population would best benefit from combination therapy and/or duration of combination therapy). According to the clinical experts, combinations with cidofovir, letermovir (off-label), and rapamycin (sirolimus) may be possible, as well. The clinical experts emphasized that maribavir cannot be combined with ganciclovir and/or valganciclovir because it has an antagonistic mechanism of action.
Considerations for discontinuation of therapy	
Should therapy end after a certain number of doses or period of time or other defined parameter?	Duration of therapy is highly individualized for refractory CMV (with or without resistance). As such, treatment discontinuation should be based on parameters that indicate clinically meaningful response, or lack thereof. The clinical experts noted that sensitives of different assays vary, and could impact utilization (e.g., number of tests) to guide treatment. For example, highly sensitive assays may require fewer confirmatory testing. In both post-SOT and post-HSCT cases, if there is end-organ disease, there should be resolution of signs and symptoms before treatment is discontinued. According to the clinical experts, clinicians generally treat patients until CMV DNA levels are low enough or negative, not for a fixed duration. Clinically meaningful response to therapy would be low CMV DNA levels and resolution of CMV end-organ disease or symptoms. CDEC discussed that 2 consecutive negative CMV PCR results obtained 1 week apart would be a reasonable way to determine when to discontinue maribavir. The clinical experts also added that if CMV levels are good, falling, and low, especially if there is toxicity with low blood cell counts or increased serum creatinine then therapy may be stopped before 2 negative tests, but the patient would be watched closely for rebound viremia.
Considerations for prescribing of therapy	
Should maribavir be limited to infectious disease specialists and/or clinicians with expertise in the management of patients who have received a transplant?	According to the clinical experts, specialists in transplant infectious disease or infectious diseases, if available, combined with the patients' primary transplant provider, are required to diagnose, treat, and monitor patients who might receive maribavir. The clinical experts also emphasized that the appropriate setting may depend on the availability of experts in a given province or region, suggesting that, for example, specialists in transplant infectious disease may not be available in some provinces so specialists in infectious disease or internal medicine may fulfill that role. However, the clinical experts maintained that clinicians with expertise in the transplant type (SOT or HSCT) and in infections must be involved. Patients who live in remote areas and have difficulties accessing specialized care may be followed remotely by relevant clinician specialists or subspecialists.
Will the diagnosis of resistant CMV infection include laboratory testing and if so, is it readily available in clinical practice?	According to the clinical experts, the diagnosis of resistant CMV infection requires laboratory testing, typically done at the National Microbiology Laboratory, and there are no concerns about availability. However, the experts noted that turnaround time is at least 10 calendar days and can exceed 2 weeks. Recognizing this potential barrier to access, CDEC noted that although testing would be performed to confirm resistance, it should not preclude patients from initiating maribavir treatment.

Implementation issues	Response
Generalizability	
There is no data available to Health Canada for pediatric patents (< 18 years); therefore, Health Canada has not authorized an indication for pediatric use. Could the clinical expert provide input for pediatric use?	The clinical experts declined to make any comments pertaining to maribavir for pediatric use, citing that their primary area of practice is in the adult population. Use of maribavir in pediatric patients is beyond the scope of this CADTH review as these patients are not included in the indication approved by Health Canada.

CMV = cytomegalovirus; HSCT = hematopoietic stem cell transplant; PCR = polymerase chain reaction; SOT = solid organ transplant.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

One open-label, randomized (2:1), double-arm, phase III trial (SOLSTICE, N = 352) was included in the CADTH systematic review. The primary objective of the SOLSTICE study was to compare the efficacy and safety of maribavir versus IAT for treatment of refractory and/or resistant CMV infection in recipients of SOT and HSCT. The trial included adult patients with documented CMV infection that is refractory to the most recent treatment or resistant to it (only if patients also met refractory criteria). Patients received 400 mg oral maribavir twice daily or another IAT (i.e., foscarnet, ganciclovir, valganciclovir, or cidofovir) for up to 8 weeks. The primary end point was confirmed CMV viremia clearance at the end of week 8 (regardless of premature treatment discontinuation). The key secondary end point was a composite of confirmed CMV viremia clearance and symptom control at the end of week 8, maintained through week 16 (8 weeks beyond the treatment phase) after receiving exclusively study-assigned treatment. Other secondary end points included recurrence, all-cause mortality, resistance to maribavir or IAT, health care resource utilization, and HRQoL. Harms outcomes were also examined. In the SOLSTICE study, both treatment groups were generally balanced but notable differences were observed in characteristics such as age, type of preparative conditioning regimen, presence of CMV resistance-associated amino acid substitutions, and CMV serostatus for the donor-recipient pairs of HSCT, CMV DNA level, and net immunosuppression use changed before initiation of study treatment.

The mean age of enrolled patients was 53.0 years (standard deviation = 13.22 years). Most patients were White (75.6%) and male (60.5%). Most patients underwent an SOT (59.9%), with the kidney (50.2% of patients who received SOT), lung (29.4% of patients who received SOT), and heart (10.9% of patients who received SOT) being the most transplanted solid organs. Patients who underwent HSCT predominantly underwent allogenic transplant procedures (99.3%). [redacted] Most patients did not have confirmed acute or chronic GVHD (91.2% and 96.9%, respectively), and did not use antilymphocyte treatment (57.7%). The majority of patients had some renal impairment (32.1% with mild and 23.3% with moderate), but no hepatic impairment (92.3%).

Efficacy Results

CMV Viremia Clearance

The primary end point was confirmed CMV viremia clearance at the end of week 8 (regardless of premature treatment discontinuation) as measured by CMV DNA levels. The adjusted difference in proportion of responders between maribavir and IAT was 32.8% (95% CI, 22.80 to 42.74; P < 0.001) in favour of maribavir (55.7% versus 23.9%).

The key secondary end point was a composite of confirmed CMV viremia clearance and symptom control at the end of week 8, maintained through week 16. The adjusted difference in proportion of responders between maribavir and IAT was 9.5% (95% CI, 2.02% to 16.88%; P = 0.013) in favour of maribavir (18.7% versus 10.3%).

Time to CMV Viremia Clearance

[redacted] The Kaplan-Meier estimate for median days to CMV viremia clearance was 22.0 days (95% CI, 21.0 days to 23.0 days) for the maribavir group and 29.0 days (95% CI, 22.0 days to 35.0 days) for the IAT group.

Recurrence

Of patients who responded to treatment, 33 (17.9%) in the maribavir group and 8 (12.3%) in the IAT group had CMV viremia recurrence during the first 8 weeks of the study. Comparative recurrence data cannot be interpreted because clearance is a prerequisite for recurrence.

All-Cause Mortality

The number of patients who died in the maribavir group was 27 (11.5%) and 13 (11.1%) in the IAT group. The median observed event time for those who died was 55.0 days (minimum = 3.0 days; maximum = 182.0 days) in the maribavir group and 73.0 days (minimum = 13.0 days; maximum = 186.0 days) in the IAT group. The hazard ratio was 1.14 (95% CI, 0.549 to 2.357). Conclusions for all-cause mortality could not be drawn because the 95% CI around the hazard ratio was wide, including the possibility of both appreciable benefit and harm for maribavir compared with IAT.

Resistance to Maribavir

[redacted]

Health Care Resource Utilization

The adjusted difference in rates ratio of hospital admissions between the maribavir and IAT groups during the on-treatment phase was 0.65 (95% CI, 0.45 to 0.94), favouring maribavir. The adjusted difference in incidence rate ratio of length of stay between the maribavir and IAT groups during the on-treatment phase was 0.46 (95% CI, 0.23 to 0.92), favouring maribavir.

HRQoL

Although HRQoL data were collected, it was only reported descriptively. Generally, patients reported an improvement in HRQoL scores (i.e., EQ-5D utility score and 36-Item Short Form Health Survey) over time and across both treatment groups. No definitive conclusions can be made between the treatment groups due to a lack of statistical testing and missing data.

Harms Results

Overall, 228 (97.4%) patients in the maribavir group and 106 (91.4%) patients in the IAT group experienced 1 or more treatment-emergent AEs. Ninety (38.5%) patients in the maribavir group and 43 (37.1%) patients in the IAT group experienced 1 or more severe AEs. Thirty-one (13.2%) patients in the maribavir group and 37 (31.9%) patients in the IAT group permanently discontinued treatment with study drugs due to AEs.

Critical Appraisal

There are limited concerns for internal validity. SOLSTICE was an open-label study. Stratified randomization was conducted using interactive response technology , suggesting allocation concealment. For the primary end point and multiple secondary end points, a central laboratory and an end point adjudication committee were appropriately used to reduce the risk of detection bias. The study population in the SOLSTICE trial was adequately defined and the clinical experts consulted by CADTH indicated that the eligibility criteria were overall appropriate. Both treatment groups were relatively balanced, with some notable differences in characteristics such as age, type of preparative conditioning regimen, presence of CMV resistance-associated amino acid substitutions and CMV serostatus for the donor-recipient pairs of HSCT, CMV DNA level, and net immunosuppression use changed before initiation of study treatment. The analysis populations used in the SOLSTICE trial were appropriate for measuring the effect of the assignment to the interventions and all analyses were pre-specified. The comparators used were identified by the clinical experts as appropriate. Statistical testing was performed for the primary and key secondary outcome. However, the open-label design can increase the risk of performance and detection bias, particularly for outcomes that are subjective in measurement and interpretation (e.g., CMV symptom controls, subjective AEs). There were some outcomes in the study for which results may be biased due missing outcome data (notably, HRQoL).

There are some implications of the trial on external validity. One stark difference between how the treatment was administered in the SOLSTICE trial and what would be expected in routine clinical practice was the 8-week fixed duration. As identified by the clinical experts consulted by CADTH for this review, clinicians treat patients until CMV DNA levels are low enough or negative, not for a fixed duration. The clinical experts indicated that the baseline characteristics of patients enrolled in the SOLSTICE trial were generally representative of the post-transplant CMV population in Canada, although they noted that patients in the SOLSTICE study would represent the most fit patients in this population, which is common in clinical trials. Furthermore, the clinical experts noted that although the comparators (i.e., IAT) used are reflective of routine clinical practice, the distribution of each IAT in the SOLSTICE trial is not reflective of Canadian clinical practice. It may be difficult to design a trial with IAT distributions that reflect the diversity of Canadian clinical practice. As a result, generalizability of results to the Canadian setting is uncertain. Moreover, conclusions on comparative efficacy for each antiviral cannot be drawn.

Other Relevant Evidence

The sponsor provided a series of additional exploratory analyses of individual patient data from the SOLSTICE trial. The results of the individual patient data analyses were used as direct inputs into the base case and scenarios of the cost-effectiveness model.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult recipients of SOT or HSCT who have refractory and/or resistant CMV infection/disease
Treatment	Maribavir
Submitted price	Maribavir, 200 mg, oral tablets: $276.7857 per tablet
Treatment cost	$58,128 per 7.5-week course of treatment (52.5 days)
Comparator	IAT comprising of IV ganciclovir, oral valganciclovir, IV foscarnet, and IV cidofovir
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (47 years)
Key data source	Treatment efficacy of the treatment and comparators were derived from the Clinical Study Report and an IPD analysis from the TAK-620-303 (SOLSTICE) trial
Key limitations	• The sponsor compared maribavir to a single comparator, IAT, that consisted of a pooled combination of antiviral therapies based on the distribution and treatment duration observed in the clinical trial. Given the lack of comparative clinical evidence for maribavir compared with individual antiviral drugs, the cost-effectiveness of maribavir relative to individual antiviral drugs remains unknown. Furthermore, the reported cost-effectiveness of maribavir to the pooled IAT comparator is highly uncertain, as the clinical experts consulted by CADTH found that the distribution and treatment duration used by the sponsor is not reflective of Canadian practice. • Different mortality rates were applied to the different health states in the first 52 weeks of the model. This approach implicitly links treatment effect to mortality, resulting in a survival benefit for patients on maribavir. However, the trial results found no clinically meaningful difference in mortality between treatment groups. • The sponsor extrapolated treatment efficacy (CMV clearance and recurrence) for weeks 20 to 52 based on trial-reported data. There is no clinical evidence of the long-term effects of maribavir on maintaining CMV clearance compared to other treatments, and the clinical efficacy of treatments used for re-treatment remains unknown. The clinical experts consulted by CADTH indicated that treatment effects would not remain constant over the initial 52 weeks. As such, the long-term cost-effectiveness of maribavir is uncertain. • The sponsor assumed that, in patients initially on maribavir, re-treatment would entail IAT. The clinical experts consulted by CADTH suggested that, in the case of CMV recurrence, re-treatment with the same initial treatment would be most likely. Therefore, by assuming a switch to IAT, the expected cost of maribavir was underestimated. • Administrative costs were deemed uncertain, both due to the sponsor assuming IV treatments would be administered in an outpatient setting and the uncertainty in the cost estimate used. A proportion of patients may require inpatient treatment, which may result in IAT costs being underestimated.
CADTH reanalysis results	• To account for the key limitations identified, several changes were made to derive the CADTH base case. This included assuming no mortality difference between treatments from week 8 onward, assuming equivalent clinical efficacies between maribavir and IAT from the end of the trial follow-up period onward, and assuming that re-treatment would occur with the same drug that was used initially.

Component	Description
	• In the CADTH base case, the ICER for maribavir compared to IAT was $403,089 per QALY gained (incremental costs = $7,429; incremental QALYs = 0.02). To be considered cost-effective at a $50,000 per QALY threshold, a price reduction of 4.5% would be required. • The model results were primarily driven by drug administration costs given that maribavir is an oral therapy that may have potential savings (e.g., supplies, chair time, nursing time) compared to IV antivirals. Although the model estimated the savings related to drug administration to be more than $70,000, the potential magnitude of that cost saving is unclear. • CADTH was unable to account for some key limitations in the sponsor's economic evaluation, including evaluating the cost-effectiveness of maribavir against individual antiviral drugs, estimating a weighted IAT comparator representative of Canadian practice, and incorporating a treatment duration reflective of Canadian practice that treats until viral clearance.

CMV = cytomegalovirus; HSCT = hematopoietic stem cell transplant; IAT = investigator-assigned treatment; ICER = incremental cost-effectiveness ratio; IPD = individual patient-level data; LY = life-year; PSM = partitioned survival model; QALY = quality-adjusted life-year; SOT = solid organ transplant.

Budget Impact

CADTH identified several limitations with the sponsor's analysis: the anticipated market uptake for maribavir in patients receiving HSCT was likely overestimated, the budget impact estimate is uncertain as treatment duration is highly variable and a key driver of analyses, and the proportion of patients eligible for public coverage is uncertain and may underestimate the budget impact if inaccurate. Lastly, the estimated target population is uncertain: the incidence of CMV viremia in patients receiving SOT and the proportion of SOT recipients who have refractory and/or resistant infections was likely underestimated, and the proportion of HSCT recipients who have refractory and/or resistant infections was likely overestimated. A CADTH reanalysis decreased the market shares for maribavir in patients receiving HSCT and adjusted the target population parameters to reflect clinical expert opinion. In the CADTH reanalysis, the estimated budget impact for maribavir was $7,811,026 in year 1, $10,073,188 in year 2, and $12,108,445 in year 3, for a 3-year total of $29,992,660. CADTH found the budget impact of maribavir to be sensitive to treatment duration, incidence of CMV viremia and proportion of those with refractory and/or resistant CMV, and proportion of patients eligible for public coverage.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting date: August 24, 2022

Regrets: Two expert committee members did not attend.

Conflicts of interest: None