Antiviral agent **April 2022**
Maribavir (Livtencity, Takeda) **Non-Formulary**

Criteria for formulary consideration of maribavir

Efficacy
Maribavir is currently approved by the FDA for use in refractory CMV infection and disease in post-transplant patients.[1-2] The current agent recommended for first line treatment of CMV is ganciclovir, but resistance to ganciclovir is increasingly becoming an issue.[3] Current guidelines recommend foscarnet or cidofovir as an agent in refractory or resistant CMV, but one of the more common gene mutations in UL97 is also resistant to foscarnet and cidofovir.[3] As shown in the phase 2 and 3 studies outlined in Table 3, maribavir has shown superiority over regimens including valganciclovir, cidofovir, foscarnet, and ganciclovir for refractory CMV treatment in HSCT and SOT.[4-7] In the phase 2 study done by Papanicolaou and colleagues, maribavir 400-1200 mg BID led to undetectable CMV viral load in 67% of patients by week 6 who had refractory CMV history.[4-5] This was followed by the phase 3 study by Avery and colleagues that showed that maribavir 400 mg BID was superior to investigator assigned anti-CMV treatment (IAT) (valganciclovir, ganciclovir, foscarnet, or cidofovir) at 8 weeks for CMV DNA clearance.[6-7]

Safety
Maribavir has no contraindications or black box warnings against use in refractory CMV post-transplant patients.[1] The main precaution for maribavir is the risk of reduced antiviral activity if used in combination with ganciclovir or valganciclovir and the potential for pUL97 resistance after maribavir use. Ganciclovir and valganciclovir require pUL97 for activation, which is the protein kinase that maribavir inhibits, leading to inactive valganciclovir and ganciclovir. Other precautions with maribavir are related to drug interactions, specifically with immunosuppressants, that require more frequent monitoring to avoid increase immunosuppressant levels and side effects.[1] Elevated immunosuppression levels and side effects were more commonly seen in maribavir treated patients compared to other therapies for treatment of CMV.[6-7] Common side effects are dysgeusia, nausea, vomiting, diarrhea, and fatigue, which resolved within a median of 6 days after therapy completion in studies. Dysgeusia was related solely to maribavir in studies, while gastrointestinal side effects were seen at equal rates among maribavir and other treatments. Serious side effects that were seen with maribavir use include neutropenia (2-4%), decreased hemoglobin (15-32%), decreased platelets (5-18%), and elevated serum creatinine (7-33%). These serious side effects occurred at higher rates in the active control arm in studies which included therapy with valganciclovir, ganciclovir, foscarnet, and cidofovir. Specifically, 33.9% of patients receiving ganciclovir or valganciclovir experienced neutropenia compared to 9.4% in the maribavir group. Additionally, renal adverse events were higher in the foscarnet group (31.9%) versus the maribavir group (15.8%). Overall, maribavir has similar rates of gastrointestinal side effects, lower rates of myelosuppression and kidney injury, and increased rates of immunosuppression level elevations when compared to other medications currently being used for CMV treatment post-transplant. [6-7]

Medication errors with maribavir due to look-a-like medication names is possible due to many other antivirals that also end with “-vir.” Other potential medication errors could occur with maraviroc (used in HIV) and maribavir and Livmarli, Lumify, Lumigan, or Lumoxiti with Livtencity.

Uniqueness
Maribavir has a unique MOA, working by inhibiting protein kinase pUL97.[1] Maribavir is a twice daily tablet that can be taken with or without meals for ease of use.[1] There are fewer monitoring parameters for maribavir than valganciclovir, foscarnet, or ganciclovir.[2] CMV DNA quantification is the main efficacy monitoring parameter required with use. For safety, monitoring is primarily needed for drug interactions. Patients receiving maribavir may be on immunosuppression, which will require levels to be drawn with initiation and dose changes of maribavir.[2] Rates of neutropenia and acute kidney injury were low in studies and should only require routine monitoring in patients that have myelosuppression or chronic kidney disease at baseline.[4-12] Overall, maribavir is an efficacious option for refractory CMV that is easy to administer and monitor both inpatient and outpatient.

Cost
Treatment options for refractory CMV include foscarnet and cidofovir, though both therapies were inferior to maribavir in a recent phase 3 study. Daily cost of foscarnet injection is slightly higher than maribavir, while cidofovir injection lower than maribavir cost due to its once weekly dosing regimen with a daily cost of $134.37.

Table 1. Cost Comparison of Agents Used in Refractory CMV

Medication	Package Size	Cost Per Dose	Daily Cost
Maribavir 64764-0800-28 64764-0800-56	200 mg tablets x 28 tablets 200 mg tablets x 56 tablets	$444.64	$889.28
Foscarnet 63323-0875-50 *60 mg/kg q8h in 85 kg patient estimates*	6000 mg/250 mL injection	$302.49	$907.47
Cidofovir 23155-0216-31 *5 mg/kg once weekly in 85 kg patient estimates*	375 mg/5 mL injection	$470.31	$134.37

Recommendations

Maribavir should be added to inpatient and outpatient formulary for use in refractory CMV patients that have undergone SOT or HSCT for its superiority in efficacy over other antiviral agents already on formulary.

The authors of this document have no financial relationship with pharmaceutical companies, biomedical device manufacturers, or distributors or others whose products or services may be considered related to the subject matter within.

Introduction
CMV is a herpesvirus that is common in most humans in the United States that can be asymptomatic or a self-limited febrile illness when the primary infection occurs.[3] Once the primary infection is complete in an immunocompetent individual, CMV will persist as a latent virus that is capable of transmission to immunosuppressed patients. Solid organ transplant (SOT) patients are often immunosuppressed and are therefore at higher risk for contracting CMV post-transplant. CMV infection and disease usually occurs within 3 months after transplant if no preventative measures are utilized and can lead to many complications and an overall decrease in survival.[3]

Table 2. Definitions of Refractory and Resistant CMV[3]

Classification	Definition	Risk Factors	Treatment
Refractory	CMV DNAemia increases or worsening in signs and symptoms after 14 days of appropriate antiviral therapy	Over-immunosuppression, subtherapeutic antiviral drug concentrations, ganciclovir resistance	Reduce immunosuppression Resistance testing of UL54 and UL97 Switch to foscarnet or increase IV ganciclovir to 10 mg/kg every 12 hours
Resistant	Presence of viral genetic mutation or alteration that decreases susceptibility to antiviral medications		

First line treatment for non-refractory CMV infection or disease is oral valganciclovir and intravenous ganciclovir. Lack of improvement after two weeks of this antiviral therapy for CMV is considered refractory CMV (see Table 2), and this can occur due to over-immunosuppressed status of a patient or resistance to antiviral drugs, such as ganciclovir.[3] Risk factors for resistant CMV include intense immunosuppression, lung transplantation, donor positive CMV with recipient negative CMV serostatus, and prolonged use of subtherapeutic doses of antivirals.[3]

If resistant CMV is of concern, genotypic resistant testing is typically performed to determine the specific mutations.[3] Commonly seen mutations leading to resistance to ganciclovir occur in the UL97 gene and are less common in the UL54 gene. When UL54 gene mutations occur, there is potential for cross-resistance to foscarnet and cidofovir, due to their pharmacological activity inhibiting UL54. Once patients are determined to have refractory and resistant CMV, the general first-line strategy is to reduce immunosuppression. If a patient has a UL97 gene mutation, foscarnet is the first-line treatment and cidofovir may have some usefulness. There have been studies to demonstrate the efficacy of these drugs in SOT patients, but there are concerns with the safety profile of these medications. Both cidofovir and foscarnet are nephrotoxic, which is a barrier to their use in SOT patients. Letermovir, a newer antiviral, has been reported in case studies to successfully treat resistant CMV, but it also has been complicated by specific UL56 mutations which inhibit its activity.[3]

There remained no clear agent for resistant CMV infection in SOT patients until the recent approval of maribavir.[1-2] Maribavir was approved by the FDA for use in refractory CMV infection and disease in post-transplant patients. Maribavir has shown superiority over regimens including valganciclovir, cidofovir, foscarnet, and ganciclovir for refractory CMV treatment in HSCT and SOT in the Phase 2 and 3 studies outlined below.[4-7] In addition to its efficacy, maribavir demonstrated a desirable safety profile with low risk of myelosuppression or nephrotoxicity which can occur with the other antiviral agents.[4-12]

Table 3. Comparison of CMV Antivirals Used In CMV[13-17]

Agent	Route	Toxicities/DDI
Maribavir	PO	Dysgeusia, GI
Ganciclovir	IV	Cytopenias
Valganciclovir	PO	Cytopenias
Foscarnet	IV	Nephrotoxicity, electrolyte wasting, GI
Cidofovir	IV	Nephrotoxicity, neutropenia, HA, uveitis/iritis, diarrhea, ocular hypotony
Letermovir	IV, PO	Nausea/ several DDIs: cyclosporine, tacrolimus/sirolimus, statins, ergot alkaloids

HA: headache, DDI: drug-drug interactions

Table 4. Pharmacokinetics[1]

Pharmacokinetic Parameters for Maribavir	
PK	Time-independent: maribavir concentrations increased dose proportionally up to 900 mg, doses greater than 900 mg twice daily showed no increase in Cmax or AUC
Absorption	T_{max} = 1 to 3 hours

	Multiple dose AUC = 128 ug*hr/mL Multiple dose C_{max} = 17.2 ug/mL
Distribution	Mean steady state volume of distribution = 27.3 L % plasma protein bound = 98%
Metabolism	CYP3A4 (major) CYP1A2 (minor) Mean half-life = 4.32 hrs
Excretion	% dose excreted (unchanged) in urine = 61%

Pharmacodynamics
In studies evaluating 400 mg to 1200 mg BID, there was no relationship between drug exposure and viral load.[1] Increased exposure does not lead to an increased chance of CMV DNA that is less than the quantifiable limit. Additionally, maribavir does not prolong the QT interval even when given at large doses that lead to double of the peak concentration seen with usual dosing.[1]

Pharmacology
Maribavir is an antiviral that works by inhibiting the cytomegalovirus enzyme pUL97, an enzyme with protein kinase activity that is involved in protein phosphorylation.[1]

FDA Approved Indications
Maribavir (Livtencity) was FDA-approved on November 23, 2021 for posttransplant cytomegalovirus treatment in patients ≥12 years old and weighing ≥35 kg refractory to treatment with ganciclovir, valganciclovir, cidofovir, or foscarnet.[2]

Clinical Trials

Table 5. Clinical Trials Evidence[4-9]

<table>
<tr><th>Study Design</th><th>Methods</th><th>Results</th><th>Conclusions/Comments</th></tr>
<tr>
<td>Clinicaltrials.gov (NCT02931539).; Trial SHP1263-303 in Integrated Review. Drugs@FDA. 2021; Avery RK, 2021.

Phase 3, multicenter, randomized, open-label, active-controlled study

Maribavir = 235, active control = 117

Intervention = maribavir 400 mg BID x 8 weeks
Active control = valganciclovir, ganciclovir, foscarnet, or cidofovir x 8 weeks

December 22, 2016 to August 17, 2020 (3 years, 9 months)</td>
<td>Inclusion Criteria
• HSCT or SOT recipient
• Documented CMV infection confirmed with 2 consecutive plasma CMV DNA assessments
• Current CMV infection refractory to anti-CMV agent (valganciclovir, ganciclovir, foscarnet, or cidofovir), defined as failure to achieve > 1 log10 decrease in CMV DNA after 14 days of treatment
• ≥ 12 years old and ≥ 35 kg
• Negative beta-HCG pregnancy test at screening if female
• EGFR > 30 mL/min/1.73m2, platelets ≥ 25000/mm3, hemoglobin ≥ 8g/L, and absolute neutrophil count≥1000/mm3

Exclusion Criteria
• Recurrent CMV refractory due to nonadherence
• Required valganciclovir, ganciclovir, foscarnet, or cidofovir for other reasons
• Elevated LFT at baseline
• HIV positive
• Mechanical ventilation or vasopressor support
• Female and pregnant or breast feeding
• Previous maribavir use
• Active malignancy
• CMV with CNS involvement
• Use of leflunomide, artesunate, or letermovir < 14 days before study start
• Chronic or acute hepatitis C

Statistical Analyses
• Primary Outcome: Cochran-Mantel-Haenszel
• Secondary Outcomes: Type 1 error rate at 5%, 95% confidence interval, time to all-cause mortality done with Kaplan-Meier method, stratified log-rank to compare groups, stratified Cox’s regression to stratify with transplant and plasma CMV level
• Safety: summary statistics</td>
<td>Primary Efficacy Variable Results
• Confirmed clearance of CMV DNA at week 8
<table>
<tr><th>Endpoint</th><th>Maribavir (n=235)</th><th>IAT (n=117)</th><th>Adjusted difference</th></tr>
<tr><td>Response</td><td>131 (56)</td><td>28 (23.9)</td><td rowspan="2">32.8 (22.8-42.74) p<0.001</td></tr>
<tr><td>Nonresponse</td><td>104 (44.3)</td><td>89 (76.1)</td></tr>
</table>
Secondary Efficacy Variable Results
• Clearance of CMV DNA and symptoms at week 8 through week 16
<table>
<tr><th>Maribavir n= 235</th><th>IAT n=117</th><th>Adjusted difference</th></tr>
<tr><td>44 (19)</td><td>12 (10)</td><td>9 (2-17) p=0.013</td></tr>
</table>
Adverse Events
• Most common cause for drug discontinuation was neutropenia (9%) and AKI (5%) with IAT group and dysgeusia (1%) and N/V/D (1% each) in maribavir group
• The mechanism of the unique side effect of dysgeusia is unknown
<table>
<tr><th>Event (%)</th><th>Maribavir n=234</th><th>IAT n=116</th></tr>
<tr><td>ADE leading to drug discontinuation</td><td>13</td><td>32</td></tr>
<tr><td>Dysgeusia</td><td>37.2</td><td>3.4</td></tr>
<tr><td>Nausea</td><td>21.4</td><td>21.6</td></tr>
<tr><td>Neutropenia</td><td>9.4</td><td>22.4</td></tr>
<tr><td>Diarrhea</td><td>18.8</td><td>20.7</td></tr>
<tr><td>Vomiting</td><td>14.1</td><td>16.4</td></tr>
</table>
</td>
<td>Author’s Conclusion: In patients with refractory, post-transplant CMV infection, maribavir 400 mg BID is a tolerable and efficacious treatment regimen with activity against resistance that many other CMV drugs do not have. Maribavir was superior to IAT in regard to CMV DNA clearance.

Comments: This study was not blinded, as it was an open-label study done by the manufacturer, which can introduce bias. To assist with controlling bias, the investigators did have an independent group to complete study statistics. Other limitations include that there were no pediatric patients included, more patients with refractory only CMV were in the maribavir group, and CMV encephalitis patients were excluded because maribavir does not cross blood brain barrier. Because this was a multicenter and randomized trial, it is generalizable to all transplant patients with refractory CMV. Despite shorter duration of therapy with all of the medications in the IAT group, there were still similar rates of ADEs experienced compared to maribavir.</td>
</tr>
</table>

<table>
<tr>
<td>Trial SHP1263-203 in Integrated Review. Drugs@FDA. 2021; Maertens 2019.

Multicenter, dose ranging, parallel group, randomized, active control phase 2 study

Maribavir 400 mg BID= 40
Maribavir 800 mg BID = 40
Maribavir 1200 mg BID = 39
All doses n=119
Valganciclovir 900 mg BID = 40

Intervention= maribavir 400 mg BID, 800 mg BID, or 1200 mg BID

May 12, 2012 to July 25, 2014</td>
<td>Inclusion Criteria
• Age ≥ 18
• Stem cell or solid organ transplant recipient
• Documented, confirmed CMV infection in only plasma or blood with viral load >1000 to <100,000 DNA copies
• CMV not known to be resistant to other antivirals
• Platelets ≥ 25,000/mm3, hemoglobin ≥ 8g/L, and absolute neutrophil count≥500/mm3
• Female and postmenopausal, sterile, or negative pregnancy screen
• Male and acceptance with birth control for up to 3 months post-study

Statistical Analyses
• Intention to treat 95% CI using Clopper-Pearson method to summarize response to therapy
• Odds ratios and CMH to compare arms of treatment
• Compared each dose of maribavir to control using stratification of baseline DNA and transplant with risk differences and two-sided Mantel-Haenszel test</td>
<td>Primary Efficacy Results
• No statistically significant difference between maribavir and valganciclovir and no dose-response difference among maribavir regimens
<table>
<tr><th></th><th>MV 400 N=40</th><th>MV 800 n=40</th><th>MV 1200 n=39</th><th>MV ALL n=119</th><th>VAL n=40</th></tr>
<tr><td>Week 3 Undetectable plasma CMV DNA</td><td>26 (65)</td><td>23 (58)</td><td>23 (59)</td><td>72 (61)</td><td>22 (55)</td></tr>
<tr><td>Comparison w/control: p value</td><td>0.2775</td><td>0.7218</td><td>0.6437</td><td>0.4107</td><td>NA</td></tr>
<tr><td>Week 6 undetectable plasma CMV DNA</td><td>31 (77.5)</td><td>33 (82.5)</td><td>28 (71.8)</td><td>92 (77.3)</td><td>26 (65)</td></tr>
<tr><td>Comparison w/control: p value</td><td>0.1712</td><td>0.0633</td><td>0.4528</td><td>0.0822</td><td>NA</td></tr>
</table>
Safety Results
• Non-fatal treatment emergent serious adverse events in 44% of maribavir and 33% in valganciclovir group
• No significant difference between treatment emergent serious adverse events with different maribavir doses, but difference in any adverse event
• Vomiting occurred in 31% in 1200 mg BID vs.10% in 400 mg BID maribavir group
• Dysgeusia most common TEAE at 40% in maribavir, followed by GI TEAE (20-23%), cough and peripheral edema (both 14%), UTI (13%), decreased appetite (12%), and headache (12%)
• Discontinuation due to adverse events was higher with maribavir at 23% versus valganciclovir group at 13%
• Leading causes for discontinuation with maribavir was CMV infection in 5% followed by N/V in 3% patients
• Dose adjustment due to ADE occurred in 8% of maribavir vs. 48% in valganciclovir
• Hgb 6.5-9.5 g/dL in 18-35% of maribavir and creatinine 1.5-2.5 mg/dL in 32% maribavir</td>
<td>Author's Conclusion: There was no statistical difference between any of the maribavir dosing groups for the outcome of undetectable plasma CMV viral load at 3 or 6 weeks. There was also no difference compared to valganciclovir. These agents may be similar in efficacy. For safety, higher doses of maribavir were associated to more vomiting than lower doses and valganciclovir required dose adjustments more frequently due to ADEs. Maribavir ≥ 400 mg BID is effective for CMV in solid organ transplant or stem cell transplant patients.

Comments: This trial being unblinded and performed by the manufacturer introduces bias. Additionally, valganciclovir appeared to have similar rates of laboratory abnormalities as maribavir, which is unexpected based on known ADEs with valganciclovir. This could have been due to the close monitoring for toxicity in this group and frequent dose reduction that occurred in 48% of patients.</td>
</tr>
<tr>
<td>Trial SHP1263-203 in Integrated Review. Drugs@FDA. 2021; Papanicolaou 2019.

Multicenter, randomized, dose ranging, parallel group phase 2 study

Intervention:
Maribavir 400 mg BID =40
Maribavir 800 mg BID = 40
Maribavir 1200 mg BID = 40

July 2012 to December 2014</td>
<td>Inclusion Criteria
• Hematopoietic stem cell transplant and solid organ transplant recipient ≥ 12 years of age
• Confirmed CMV infection refractory to treatment with an FDA-approved CMV treatment (defined as inability to decrease viral load by ≥ 1 log10 by 2 weeks of therapy)
• CMV viral load of ≥ 1,000 copies/mL

Statistical Analyses
• No plan for statistical analysis due to small, anticipated enrollment
• Summary analyses done for treatment effect and dose effect
• Kaplan Meier used for analysis of time to event</td>
<td>Primary and Secondary Efficacy Results
• 67% of patients had undetectable CMV viral load at 6 weeks
<table>
<tr><th>Outcome</th><th>MV 400 BID n=40</th><th>MV 800 BID n=40</th><th>MV 1200 BID n=40</th><th>ALL MV Doses n=120</th></tr>
<tr><td>Undetectable CMV in plasma in 6 weeks n (%)</td><td>28 (70)</td><td>25 (62.5)</td><td>27 (67.5)</td><td>80 (66.7)</td></tr>
<tr><td>CMV recurrence after undetectable viral load</td><td>7/29 (24.1)</td><td>11/27 (40.7)</td><td>12/30 (40)</td><td>30/86 (34.9)</td></tr>
</table>
Safety
• Dysgeusia occurred in 65% of patients overall, with it most commonly occurring in 1200 mg BID group at 72.5% vs 60% in 400 mg BID group
• N/V were common ADE occurring in 34.2 and 29.2% of patients overall, respectively
• Diarrhea was 25-32.5% in higher dose MV groups vs. 12.5% in 400 mg BID dose group
• Most common ADE leading to discontinuation was CMV infection (42% of discontinuations) with NVD only leading to discontinuation in 3 patients overall
• Neutropenia occurred in 11% of patients, but there was baseline neutropenia in 16% of patients</td>
<td>Authors Conclusion: Maribavir 400-1200 mg BID led to undetectable CMV viral load in 67% of patients by week 6 that had refractory CMV history.

Comments: This study had small sample sizes among different doses of maribavir, so it is hard to say if there were truly differences or no differences among dosing for safety events. This study is limited by not having a control arm and small cohort sizes. The different dosing regimens may have also compromised the blinding, leading to potential bias.</td>
</tr>
<tr>
<td colspan="4">Abbreviations: IAT: Investigator assigned anti-CMV; ADE = adverse event; TEAE: treatment emergent adverse event; Hgb: hemoglobin; MV: maribavir, CI: confidence interval; CMV: cytomegalovirus
NVD: nausea, vomiting, diarrhea; CMH: Cochran-Mantel-Haenszel</td>
</tr>
</table>

Table 6. Clinical Trials: Maribavir for Prophylaxis[10-12]

First Author, date	Phase	Population	Primary/Secondary Outcome	Result	Notes
Winston, 2008	2	Inclusion • Adults ≥ 18 years of age with CMV IgG positive before transplant and were receiving their first allogeneic stem cell transplant • Evidence of transplant engraftment, no detectable CMV infection, no previous post transplantation CMV therapy Exclusion • HIV, renal insufficiency, hepatic dysfunction, severe GI issues including NVD	Primary outcome: incidence and onset time of CMV disease or infection Secondary: incidence of CMV disease, antiviral CMV infection usage Safety: ADE, mortality, changes in labs	N=111 (28 placebo, 28 **maribavir 100 mg BID**, 28 maribavir 400 mg once daily, 28 maribavir 400 mg BID) Incidence of CMV infection or disease based within 100 days on pp65 antigenemia was statistically lower in the 100 mg BID group compared to placebo (p=0.046). Overall incidence was lower in 100 mg BID (15%), 400 mg once daily (19%), and 400 mg BID (15%) compared to placebo at 39% incidence. Incidence of CMV infection or disease based on positive CMV DNA PCR was statistically significantly lower in all 3 maribavir dosing groups compared to placebo. Time to CMV was associated with significant reduction in all 3 maribavir dosing arms compared to placebo. ADE most frequent with highest dose group of 400 mg BID at 54% of patients experiencing and 35% discontinuing therapy due to ADE. Most common ADE were taste disturbances and NV, which were also the leading causes of discontinuation overall.	Maribavir reduced CMV infection at 100 days compared to placebo based on CMV DNA PCR. This study only looked at 100 days post-transplant. Statistical significance only seen with PCR CMV DNA testing. Limited by small study population.
Marty, 2011	3	Inclusion • Adults older than 18 years of age who had received allogenic stem-cell transplants with recipient or donor seropositive CMV • Maribavir had to be started 14-30 days post-transplant • Evidence of engraftment, no detectable CMV infection Exclusion • History of CMV disease within 6 months prior to randomization, CMV treatment after transplant, severe hepatic or renal dysfunction	Primary: incidence of CMV disease within 6 months post-transplant Secondary: incidence and time of CMV infection onset, onset of CMV disease, pre-emptive therapy or treatment of CMV initiation Safety: ADE, mortality, change in labs	**Maribavir 100 mg BID** N=454 and placebo N=227 Incidence of CMV disease at 6 months post-transplant was not statistically different between the groups. (p=0.79) Incidence of CMV infection or disease based within 100 days on pp65 antigen was statistically lower in maribavir group (p=0.02), but not at 6 months Incidence of CMV infection or disease based on positive CMV DNA PCR was not statistically different between groups at 100 days or 6 months. Time to CMV treatment was longer in maribavir group than placebo at 100 days (p=0.07) but not at 6 months. Acute GVHD was leading ADE at 33-36% in placebo and maribavir group. This was followed by diarrhea, fatigue, and nausea. Dysgeusia occurred in 15% of maribavir vs. 6% placebo.	Maribavir did not prevent CMV when compared to placebo. Lower rates of taste disturbance found which is likely due to lower dose utilized of 100 mg BID. Lower dose utilization might have been a reason for failure. Patients did not start therapy until around 24 days post-transplant, which may be too long and insufficient for preventing CMV. This study looked at outcomes at 6 months versus 100 days like previous Winston 2008 study. This study did not include infection AND disease in primary outcome like previous Winston 2008 study, which could be why it did not see differences.
Winston, 2012	3	Inclusion • Orthotopic liver transplant recipients ≥ 18 years of age that are CMV-seronegative with CMV-seropositive donor • Maribavir started within 10 days post-transplant and no detectable CMV infection post-transplant Exclusion • History of CMV disease of any organ within 6 months prior to study, CMV treatment at time of study start, CrCl < 10 mL/min, dialysis, HIV, mechanical ventilation, repeat liver transplant or multiorgan transplant	Primary: incidence of CMV disease by 6 months post-transplant (including CMV organ disease or symptomatic infection) Secondary: time to onset of CMV disease, incidence and time to onset of CMV infection, pre-emptive therapy or treatment of CMV initiation	**Maribavir 100 mg BID** with acyclovir 400 mg BID N=174 OR ganciclovir 100 mg TID N=174 CMV disease within 6 months after transplant occurred in 8% of ganciclovir patients versus 12% of maribavir patients, showing no significant difference between therapies. No difference in time to onset of CMV disease within 6 months between groups. (p=0.2371) Within 100 days after transplant, CMV disease incidence was statistically higher in maribavir group at 9% versus 0% in ganciclovir. (p-0.0007) Ganciclovir had significantly lower incidence of CMV infection at 100 days (all p<0.0001) and 6 months after transplant. Ganciclovir also had significantly lower initiation of anti-CMV therapy at 100 days (p<0.0001). Diarrhea was most common ADE, dysgeusia was similar between groups. Hematological ADEs were more common with ganciclovir than maribavir with statistically lower amount of neutropenia in maribavir group. (p<0.05)	Study stopped early because clear superiority of ganciclovir over maribavir. Maribavir at 100 mg BID is inappropriate and not efficacious for CMV prophylaxis in liver transplant. This was done in liver transplant versus two other studies in stem cell transplant.

Table 7. Clinical Trial Summary[4-12]

Literature Review Summary on Maribavir Use		
Indication	Population	Summary
Prophylaxis	Hematopoietic Stem Cell Transplant with seropositive CMV donor or recipient Liver transplant with CMV seropositive donor	Maribavir was shown to be statistically superior to placebo at all doses for CMV prevention at 100 days in a small phase 2 trial in hematopoietic stem cell transplant (HSCT) published in 2008, but in 2011 a phase 3 trial showed differing results.[10-11] At 100 days and 6 months post-HSCT, rates of CMV were no different in placebo group versus maribavir 100 mg BID group.[11] Additionally, a phase 3 study published in 2012 comparing ganciclovir to maribavir for CMV prevention in liver transplant was stopped early due to clear superiority of ganciclovir on CMV prevention.[12] Therefore, maribavir is not recommended for use as a prophylactic CMV agent in (solid organ transplant) SOT or HSCT.
Treatment of CMV infection	HSCT or SOT CMV infection with NO resistance	Maertens and colleagues in 2019 showed that for HSCT or SOT patients with a non-resistant CMV infection, maribavir at all doses was not statistically different than valganciclovir for undetectable CMV viral load at 3 or 6 weeks.[8-9] Rate of vomiting ADE was higher in the higher doses of maribavir and valganciclovir was dose adjusted more commonly due to ADE. Maribavir at doses ≥ 400 mg BID was comparable to valganciclovir for CMV treatment in SOT or HSCT patients.[8-9]
Treatment of resistant or refractory CMV infection	HSCT or SOT CMV infection refractory to anti-CMV agent (valganciclovir, ganciclovir, foscarnet, or cidofovir)	In the phase 2 study done by Papanicolaou and colleagues, maribavir 400-1200 mg BID led to undetectable CMV viral load in 67% of patients by week 6 who had refractory CMV history.[4-5] This was followed by the phase 3 study by Avery and colleagues that showed that maribavir 400 mg BID was superior to IAT (valganciclovir, ganciclovir, foscarnet, or cidofovir) at 8 weeks for CMV DNA clearance. [6-7]

Table 8. Ongoing Clinical Trials for Maribavir[18-20]

Trial and Progress	Design and Maribavir Role Being Tested	Study Arms
Clinicaltrials.gov. NCT02927067.; Trial SHP1263-302 in Integrated Review. Drugs@FDA. 2021. Active, not recruiting yet	Phase 3 double blind, double-dummy, active controlled, multicenter, RCT Stem cell transplant patients with CMV infection	Maribavir 400 mg BID Valganciclovir 900 mg BID Placebo BID *All for 8 weeks*
Clinicaltrials.gov. NCT05137717. Recruiting	Phase 3 open label, single arm study Stem cell or solid organ transplant Japanese patients with CMV infection	Maribavir 400 mg BID x 8 weeks
Clinicaltrials.gov. NCT05319353. Not yet recruiting, first posted April 8, 2022	Phase 3 open label, single arm study Children and adolescents who have received stem cell transplant or solid organ transplant and need CMV infection treatment	Maribavir 200-400 mg BID based on body weight, patients 0-6 dosing based on PK modeling

Warnings, Precautions, and Adverse Effects

Table 9. Warnings, Precautions, and Adverse Effects of Maribavir[1,2]

Warnings and Precautions	
Virologic failure and relapse	Virologic failure can occur with Maribavir due to resistance of the pUL97 enzyme. Within 4 to 8 weeks after discontinuing treatment, it is also possible that relapse can occur. In these cases, cross-resistance with ganciclovir and valganciclovir has been noted. Monitor CMV levels to verify patient is responding to treatment and does not relapse.
Adverse Reactions (% Incidence) (2)	
Taste disorder	46
Infection	23
Nausea	21
Diarrhea	19
Decreased hemoglobin 6.5-9.5 g/dL	15-32
Vomiting	14
Fatigue	12
Decreased platelets	5-18
Elevated creatinine	7-33
Pregnancy and Lactation	
Pregnancy	No human data to assess safety. In animal data, rats exposed to doses lower than human doses of maribavir experienced decreased embryo-fetal survival, but rabbits did not.
Lactation	No human or animal data to assess safety. It is unknown if maribavir or metabolites are present in milk or if there are effects on the newborn being breastfed.

Interactions

Table 10. Interactions with Maribavir[1,2]

Drug	Result	Recommendation
CYP3A4 inducers	Decreases maribavir concentration	Avoid combination
CYP3A4 and P-glycoprotein substrates	Decreases substrate concentration	Monitor therapy
Digoxin	Increases digoxin concentration	Monitor digoxin concentration. Reduce dose if necessary.
Carbamazepine	Decreases maribavir concentration	Maribavir 800 mg BID
Phenytoin/Fosphenytoin	Decreases maribavir concentration	Maribavir 1200 mg BID
Phenobarbital	Decreases maribavir concentration	Maribavir 1200 mg BID
Primidone	Decreases maribavir concentration	Maribavir 1200 mg BID
Rifabutin	Decreases maribavir concentration	Avoid combination
Rifampin	Decreases maribavir concentration	Avoid combination
St. John's Wort	Decreases maribavir concentration	Avoid combination
Ganciclovir/Valganciclovir	Diminished Ganciclovir/ Valganciclovir effect	Avoid Combination
Rosuvastatin	Increases rosuvastatin concentration	Monitor for rosuvastatin adverse effects like myopathy.
Cyclosporine	Increases maribavir concentration	Monitor immunosuppressant levels and adjust dose if necessary.
Everolimus	Increases maribavir concentration	Monitor immunosuppressant levels and adjust dose if necessary.
Sirolimus	Increases maribavir concentration	Monitor immunosuppressant levels and adjust dose if necessary.
Tacrolimus	Increases maribavir concentration	Monitor immunosuppressant levels and adjust dose if necessary.

Dosage and Administration

Table 11. Dosing[2]

Scenario	Dosing Regimen
Refractory CMV Treatment Adult Dosing	400 mg PO BID
Geriatric	Utilize adult dosing
Mild, moderate, or severe kidney impairment	No dosage adjustments
End-stage renal disease on dialysis	Has not been studied
Mild or moderate hepatic impairment (Child-Pugh A or B)	No dosage adjustments
Severe hepatic impairment (Child-Pugh C)	Has not been studied
Pediatric ≥ 12 years of age	Utilize adult dosing

Administration: Maribavir tablets should be taken orally with or without food.[2]

Monitoring Parameters

Table 12. Monitoring Parameters for Maribavir[2]

Lab Parameter	Available at UNMC
CMV DNA level	Yes
Immunosuppression levels	
Tacrolimus	Yes
Everolimus	Yes
Cyclosporine	Yes
Sirolimus	Yes

Cost

Table 13. Maribavir Cost Inpatient

Medication	Package Size	Cost Per Dose	Daily Cost
Maribavir 64764-0800-28 64764-0800-56	200 mg tablets x 28 tablets 200 mg tablets x 56 tablets	$444.64	$889.28

Storage

Maribavir should be stored at 20 to 25 degrees C. Exposure to environments 15 to 30 degrees C is allowed for brief periods of time.[1-2]

Prepared by: Sarah Blocker, PharmD
Reviewed by: Emily Kreikemeier, MPH, PharmD, BCPS

Appendix: Summary of Safety Issues and Implications for Pharmacy Operations

Characteristic	Summary
Medication Information	
Drug generic name (brand name)	Maribavir (Livtencity)
Drug manufacturer	Takeda Pharmaceuticals America, Inc.
Schedule of medication	None
Anticipated use per month, anticipated patient population	1-2 patients
Route of administration	Oral
Preparation (for pharmacy personnel)	None
Is bedside dilution appropriate?	No ☒ Yes ☐ NA
Stability	Store at 68 F to 77 F. Short exposure in 59 F to 86 F is allowed.
Recommended storage conditions for medication, and how to manage excursions outside these conditions	See above.
Does the manufacturer require patients to meet specific criteria for treatment with this medication? If so, where may healthcare providers find these criteria?	No
Operations Information	
Is filtration required during preparation or administration of the IV medication?	No ☐ Yes ☐ N/A ☒

*If **yes** for administration, ensure Willow adds filter information to admin instructions*	
Can medication doses be sent to patient care units via pneumatic tube system? See IC24. *If **no**, and not already addressed in IC24, add to policy IC24—contact Theresa Micheels.*	No ☐ Yes ☒ N/A ☐
Does the manufacturer have a restricted or special distribution program? If so, how may healthcare providers contact the program?	No ☒ Yes ☐
Safety/Policy Information	
Will this impact a dynamic alternative alert?	No ☒ Yes ☐
Is the medication (brand name, generic name, product packaging) similar to any other medications on the Institute for Safe Medication Practices (ISMP) Look-Alike-Sound-Alike (LASA)) list or confused names list? If not, is the medication expected to be added to the list? https://www.ismp.org/tools/tallmanletters.pdf http://www.ismp.org/Tools/confuseddrugnames.pdf	No ☒ Yes ☐
Does the product package insert currently have any boxed warnings? For what?	No ☒ Yes ☐
Is this medication a hazardous agent? *If **yes**, Med Safety to update policy MM10 Attachment A*	No ☒ Yes ☐
Is this medication classified as chemotherapy per AHFS 10:00? *If **yes**, Drug Policy to update policy MM11 Attachment A*	No ☒ Yes ☐
Is the medication a vesicant or irritant? *If **yes**, ensure Willow flags as vesicant or irritant on MAR.*	No ☒ Yes ☐
Is this a high-alert medication that requires an indication? See MM02. *If **yes**, Med Safety to update policy MM02*	No ☒ Yes ☐
Are there contraindications or significant warnings against medication use?	No ☒ Yes ☐
Is special administration or monitoring recommended when starting therapy with this medication (eg. Telemetry, BPetc)? *If **yes,** Med Safety to review at Medication Management Committee*	No ☒ Yes ☐
Is there unique dosing with administration (titration, guidance for determining dose, etc.)	No ☒ Yes ☐
Is this medication on the ISMP “Do Not Crush” list?	No ☒ Yes ☐
Does this medication require a Central Line for administration?	No ☒ Yes ☐
Is this medication infused via an infusion pump? *If **yes**, Med Safety to add to infusion pump library*	No ☒ Yes ☐
Is there a Risk Evaluation and Management Strategy (REMS) program for the medication? If so, where may healthcare providers find these criteria?	No ☒ Yes ☐
Does the medication require precautions for disposal? What kind? See EC20 Disposal of Pharmaceutical Products; EC11 Chemo Drugs-Safety Precautions for Administration	No ☒ Yes ☐
Does this medication need to be considered for auto-wasting on the MAR or another avenue for documenting waste?	No ☒ Yes ☐
Will the medication be restricted: • To a specific level of care (LOC)? See TX 24: Admission, Transfer and Discharge for Defined Levels of Care. • To a specific location? • To specific services/ providers? • To providers credentialed in deep sedation or general anesthesia? • To patients who are on the medication prior to admit?	 No ☒ Yes ☐ Unknown ☐ No ☒ Yes ☐ Unknown ☐ No ☐ Yes ☒ Unknown ☐ No ☒ Yes ☐ Unknown ☐ No ☒ Yes ☐ Unknown ☐

References:

1. Livtencity (maribavir) [package insert]. In: Drugs@FDA Online. Lexington, MA: Takeda Pharmaceuticals; 2021.
2. Maribavir. In: Lexi-Drugs Online. Hudson (OH): Lexi-Comp, Inc.; [updated 3/29/22, accessed 4/7/22].
3. Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients-Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019 Sep;33(9):e13512. doi: 10.1111/ctr.13512. Epub 2019 Mar 28. PMID: 30817026.
4. Shire (Takeda Pharmaceuticals). Livtencity Integrated Review Trial SHP620-202. In: Drugs@FDA Online. US Food and Drug Adminsitration. 2021 - [cited 2022 Apr 8]. Available from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/215596Orig1s000IntegratedR.pdf.
5. Papanicolaou GA, Silveira FP, Langston AA, et al. Maribavir for Refractory or Resistant Cytomegalovirus Infections in Hematopoietic-cell or Solid-organ Transplant Recipients: A Randomized, Dose-ranging, Double-blind, Phase 2 Study. Clin Infect Dis. 2019;68(8):1255-1264. doi:10.1093/cid/ciy706. PMID 30329038.
6. Shire (Takeda Pharmaceuticals). Efficacy and Safety Study 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. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2021- [cited 2022 Apr 8]. Available from: https://clinicaltrials.gov/ct2/show/NCT02931539. NLM Identifier: NCT02931539.
7. 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 [published online ahead of print, 2021 Dec 2]. *Clin Infect Dis.* 2021;ciab988. doi:10.1093/cid/ciab988. PMID: 34864943.
8. Shire (Takeda Pharmaceuticals). Livtencity Integrated Review Trial SHP620-203. In: Drugs@FDA Online. US Food and Drug Adminsitration. 2021 - [cited 2022 Apr 8]. Available from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/215596Orig1s000IntegratedR.pdf.
9. Maertens J, Cordonnier C, Jaksch P, et al. Maribavir for Preemptive Treatment of Cytomegalovirus Reactivation. *N Engl J Med.* 2019;381(12):1136-1147. doi:10.1056/NEJMoa1714656. PMID 31532960.
10. Winston DJ, Young JA, Pullarkat V, Papanicolaou GA, Vij R, Vance E, Alangaden GJ, Chemaly RF, Petersen F, Chao N, Klein J, Sprague K, Villano SA, Boeckh M. Maribavir prophylaxis for prevention of cytomegalovirus infection in allogeneic stem cell transplant recipients: a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. Blood. 2008 Jun 1;111(11):5403-10. doi: 10.1182/blood-2007-11-121558. Epub 2008 Feb 19. PMID: 18285548; PMCID: PMC5726327.
11. Marty FM, Ljungman P, Papanicolaou GA, Winston DJ, Chemaly RF, Strasfeld L, Young JA, Rodriguez T, Maertens J, Schmitt M, Einsele H, Ferrant A, Lipton JH, Villano SA, Chen H, Boeckh M; Maribavir 1263-300 Clinical Study Group. Maribavir prophylaxis for prevention of cytomegalovirus disease in recipients of allogeneic stem-cell transplants: a phase 3, double-blind, placebo-controlled, randomised trial. Lancet Infect Dis. 2011 Apr;11(4):284-92. doi: 10.1016/S1473-3099(11)70024-X. Epub 2011 Mar 21. Erratum in: Lancet Infect Dis. 2011 May;11(5):343. PMID: 21414843.
12. Winston DJ, Saliba F, Blumberg E, Abouljoud M, Garcia-Diaz JB, Goss JA, Clough L, Avery R, Limaye AP, Ericzon BG, Navasa M, Troisi RI, Chen H, Villano SA, Uknis ME; 1263-301 Clinical Study Group. Efficacy and safety of maribavir dosed at 100 mg orally twice daily for the prevention of cytomegalovirus disease in liver transplant recipients: a randomized, double-blind, multicenter controlled trial. Am J Transplant. 2012 Nov;12(11):3021-30. doi: 10.1111/j.1600-6143.2012.04231.x. Epub 2012 Sep 4. Erratum in: Am J Transplant. 2013 Feb;13(2):529. PMID: 22947426.
13. Valganciclovir. In: Lexi-Drugs Online. Hudson (OH): Lexi-Comp, Inc.; [updated 4/9/22, accessed 4/12/22].
14. Ganciclovir. In: Lexi-Drugs Online. Hudson (OH): Lexi-Comp, Inc.; [updated 1/16/22, accessed 4/12/22].
15. Foscarnet. In: Lexi-Drugs Online. Hudson (OH): Lexi-Comp, Inc.; [updated 4/11/22, accessed 4/12/22].
16. Cidofovir. In: Lexi-Drugs Online. Hudson (OH): Lexi-Comp, Inc.; [updated 4/4/22, accessed 4/12/22].
17. Letermovir. In: Lexi-Drugs Online. Hudson (OH): Lexi-Comp, Inc.; [updated 3/18/22, accessed 4/12/22].
18. Takeda Pharmaceuticals. A Study of Maribavir Compared to Valganciclovir to Treat Cytomegalovirus Infections in People Who Have Received Stem Cell Transplants. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2021- [cited 2022 Apr 11]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02927067?cond=NCT02927067&draw=2&rank=1.NLM Identifier: NCT02927067.
19. A Study of Maribavir in Japanese People With Cytomegalovirus (CMV) Infection. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2021- [cited 2022 Apr 11]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT05137717?term=maribavir&draw=2&rank=1.NLM Identifier: NCT05137717.
20. Takeda Pharmaceuticals. A Study to Evaluate the Safety and Tolerability, Pharmacokinetics, and Antiviral Activity of Maribavir for the Treatment of Children and Teenage Transplant Recipients With CMV. . In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2021- [cited 2022 Apr 11]. Available from: Infectionhttps://www.clinicaltrials.gov/ct2/show/NCT05319353?term=maribavir&draw=2&rank=2NCT05319353.