

# Maribavir (LIVTENCY)

## National Drug Monograph

### SEP 2022

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

*The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.*

## FDA Approval Information

### Description/Mechanism of Action

- Maribavir is a benzimidazole riboside antiviral that was approved by the United States Food and Drug Administration (FDA) on 11/23/21 for the treatment of post-transplant Cytomegalovirus (CMV), refractory to conventional antiviral therapies.<sup>1</sup>
- The mechanism of action of maribavir is to competitively inhibit the protein kinase activity of human CMV phosphotransferase or gene UL97, resulting in inhibition of phosphorylation of proteins and CMV replication<sup>1</sup>
- Mechanisms of resistance to maribavir include:
  - Mutations in UL97 gene of CMV<sup>2</sup>

### Indication(s) Under Review in This Document

- Treatment of adult and pediatric ( $\geq 12$  years and  $\geq 35$  kg) patients with post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir, or foscarnet

### Dosage Form(s) Under Review/Dosing

- Tablet, 200 mg
- Dose: 400 mg (two 200 mg tablets) by mouth (PO) BID, with or without food
- Dose adjustment needed when co-administered with CYP-inducing anticonvulsants
  - 800 mg (four 200 mg tablets) PO BID (if co-administered with carbamazepine)
  - 1200 mg (six 200 mg tablets) PO BID (if co-administered with phenytoin or phenobarbital)

## Clinical Evidence Summary

### Efficacy Considerations

- The treatment of CMV is dependent on targeting DNA polymerase encoded by gene UL94 and protein kinase encoded by UL97 to stop CMV replication
  - Until maribavir, available therapies for CMV including valganciclovir/ganciclovir, foscarnet, and cidofovir that target gene UL54 were limited by CMV resistance and toxicity
  - On efficacy of preferred/alternative agents and resistance<sup>2,3</sup>
    - Mutations to product of UL54 binding or catalytic site confers resistance of CMV to valganciclovir/ganciclovir, foscarnet, and cidofovir
    - Mutations to product UL97 substrate binding or phosphate transfer site confers resistance of CMV to valganciclovir/ganciclovir
  - On toxicity<sup>2</sup>

- Valganciclovir/ganciclovir can cause clinically relevant bone marrow suppression and nephrotoxicity
    - Foscarnet, and cidofovir can cause clinically relevant nephrotoxicity leading to proximal tubular cell injury and acute renal failure
  - Maribavir is an attractive therapeutic option as it does not have cross-resistance or similar toxicity to other therapies<sup>3</sup>
    - Does not act on product UL54 and efficacy is unaffected by UL54 mutations
    - Unlike valganciclovir/ganciclovir, maribavir targets a different location on product UL97 and does not require intracellular processing, so CMV strains that have mutated to be resistant valganciclovir/ganciclovir may or may not affect maribavir
- Based on maribavir’s proposed efficacy and safety profile, it was studied for CMV **prophylaxis, preemptive treatment, and treatment of refractory CMV** (with or without phenotypic resistance)
  - **Prophylaxis:** all patients receive therapy prophylaxis with routine PCR monitoring
    - Phase 2 trials failed to show efficacy<sup>4,5</sup>
  - **Preemptive:** all patients received routine PCR monitoring and therapy initiated if positive
    - Supported by phase 2 trial (see efficacy Table 1 below)<sup>6</sup>
  - **Treatment:** all patients receive therapy if PCR positive
    - Supported by phase 2 and 3 trials (see efficacy Table 1 below)<sup>7,8</sup>

**Table 1: Efficacy results from clinical trials<sup>6-8</sup>**

Study	Design, Purpose, Interventions	Demographics	Results
Maertens (2019) <sup>6</sup> • Phase 2 study	<p><b>Design:</b> Multicenter, randomized, open-label, dose-ranging, parallel-group study</p> <p><b>Purpose:</b> Dose-ranging safety/efficacy of maribavir versus valganciclovir for preemptive treatment of CMV infection</p> <p><b>Interventions:</b></p> <ul style="list-style-type: none"> <li>• MBV1: Maribavir 400 mg PO BID x12 weeks (n=40)</li> <li>• MBV2: Maribavir 800 mg PO BID x12 weeks (n=40)</li> <li>• MBV3: Maribavir 1200 mg PO BID x12 weeks (n=39)</li> <li>• VGC: Valganciclovir 900 mg PO BID x12 weeks (n=40)</li> </ul> <p><u>Key Inclusion Criteria</u></p> <ul style="list-style-type: none"> <li>• Adult hematopoietic-cell/solid-organ transplant recipients</li> <li>• CMV DNA 1000-100,000 copies/mL (blood or plasma)</li> </ul> <p><u>Key Exclusion Criteria</u></p> <ul style="list-style-type: none"> <li>• CMV end organ disease</li> <li>• Genotypically resistance to ganciclovir, valganciclovir, foscarnet, or cidofovir</li> </ul>	<p><u>Demographics</u></p> <ul style="list-style-type: none"> <li>• Median age               <ul style="list-style-type: none"> <li>- MBV1: 56.5</li> <li>- MBV2: 58.5</li> <li>- MBV3: 58</li> <li>- VGC: 58.5</li> </ul> </li> <li>• White, %               <ul style="list-style-type: none"> <li>- MBV1: 92</li> <li>- MBV2: 92</li> <li>- MBV3: 100</li> <li>- VGC: 80</li> </ul> </li> </ul>	<p><b>MBV 400 mg BID had efficacy similar to VGC for clearing CMV viremia.</b></p> <p><u>Secondary Outcomes (efficacy)</u></p> <p>CMV clearance, week 6</p> <ul style="list-style-type: none"> <li>• MBV 78.6% vs VGC 66.7%</li> </ul> <p>CMV recurrence</p> <ul style="list-style-type: none"> <li>• MBV 22% vs VGC 18%</li> </ul>

<p>Papanicolaou (2019)<sup>7</sup></p> <ul style="list-style-type: none"> <li>Phase 2 study</li> </ul>	<p><b>Design:</b> Multicenter, double-blind, dose-ranging RCT</p> <p><b>Purpose:</b> dose-finding efficacy, safety in transplant recipients with refractory or resistant (RR) CMV infections</p> <p><b>Interventions:</b></p> <ul style="list-style-type: none"> <li>MBV1: Maribavir 400 mg PO BID x24 weeks (n=40)</li> <li>MBV2: Maribavir 800 mg PO BID x24 weeks (n=40)</li> <li>MBV3: Maribavir 1200 mg PO BID x24 weeks (n=40)</li> </ul> <p><b>Key Inclusion Criteria</b></p> <ul style="list-style-type: none"> <li>Hematopoietic-cell transplant (HCT) and solid-organ transplant (SOT) recipients <math>\geq 12</math> years</li> <li>Documented CMV infection RR <math>\geq 1</math> FDA approved antiviral</li> <li>CMV DNA level <math>\geq 1000</math> copies/mL</li> </ul> <p><b>Key Exclusion Criteria</b></p> <ul style="list-style-type: none"> <li>Suspected non-adherence</li> <li>Receiving another antiviral when maribavir initiated</li> </ul>	<p><b>Demographics</b></p> <ul style="list-style-type: none"> <li>Median age <ul style="list-style-type: none"> <li>MBV1: 54.5</li> <li>MBV2: 61</li> <li>MBV3: 50.5</li> </ul> </li> <li>White, % <ul style="list-style-type: none"> <li>MBV1: 80</li> <li>MBV2: 77.5</li> <li>MBV3: 80</li> </ul> </li> <li>SOT, % <ul style="list-style-type: none"> <li>MBV1: 60</li> <li>MBV2: 60</li> <li>MBV3: 62.5</li> </ul> </li> <li>CMV organ disease, % <ul style="list-style-type: none"> <li>MBV1: 15%</li> <li>MBV2: 17.5%</li> <li>MBV3: 7.5%</li> </ul> </li> <li>CMV resistant to ganciclovir or foscarnet <ul style="list-style-type: none"> <li>MBV1: 55%</li> <li>MBV2: 62.5%</li> <li>MBV3: 60%</li> </ul> </li> <li>Immunosuppression reduced prior to starting MBV <ul style="list-style-type: none"> <li>MBV1: 32.5%</li> <li>MBV2: 40%</li> <li>MBV3: 40%</li> </ul> </li> </ul>	<p><b>MBV 400 mg BID is active against RR CMV infections. Treatment emergent resistance was observed while on maribavir.</b></p> <p><b>Primary Outcome</b> Undetectable plasma CMV DNA</p> <ul style="list-style-type: none"> <li>MBV1 70% vs MBV2 62.5% vs MBV3 67.5%</li> </ul> <p><b>Secondary Outcomes</b> CMV recurrence in patients on treatment</p> <ul style="list-style-type: none"> <li>MBV1 20.7% vs MBV2 33.3% vs MBV3 33.3%</li> <li><b>13 developed mutations conferring maribavir resistance</b></li> </ul> <p>CMV recurrence in patients off treatment</p> <ul style="list-style-type: none"> <li>MBV1 3.4% vs MBV2 7.4% vs MBV3 6.7%</li> </ul> <p><b>Maribavir was discontinued due to adverse events in 41/120 (34%) patients</b></p>
<p>Avery (2021)<sup>8</sup></p> <ul style="list-style-type: none"> <li>Phase 3 study</li> </ul>	<p><b>Design:</b> Multicenter open label, dose-ranging RCT</p> <p><b>Purpose:</b> Assess the safety and efficacy of maribavir for refractory CMV infections with or without resistance</p> <p><b>Interventions:</b></p> <ul style="list-style-type: none"> <li>MBV: Maribavir 400 mg PO BID x8 weeks (n=235)</li> <li>IAT: Investigator-assigned therapy with valganciclovir, ganciclovir, foscarnet, or cidofovir x8 weeks (n=117)</li> </ul> <p><b>Key Inclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>Hematopoietic cell (HCT) or solid organ transplant (SOT) recipients <math>\geq 12</math> years</li> <li>CMV DNA level <math>&gt;910</math> copies/mL</li> </ul> <p><b>Key Exclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>Suspected non-adherence</li> <li>CMV disease with CNS involvement or retinitis</li> <li>Receiving another antiviral with maribavir</li> <li>Previously received maribavir</li> </ul>	<p><b>Demographics</b></p> <ul style="list-style-type: none"> <li>Median age <ul style="list-style-type: none"> <li>MBV: 57</li> <li>IAT: 54</li> </ul> </li> <li>White, % <ul style="list-style-type: none"> <li>MBV: 76.2</li> <li>IAT: 74.4</li> </ul> </li> <li>SOT, % <ul style="list-style-type: none"> <li>MBV: 60.4</li> <li>IAT: 59</li> </ul> </li> <li>HCT, % <ul style="list-style-type: none"> <li>MBV: 39.6</li> <li>IAT: 41</li> </ul> </li> <li>CMV infection without resistance, % <ul style="list-style-type: none"> <li>MBV: 40.9</li> <li>IAT: 29.1</li> </ul> </li> </ul>	<p><b>Primary Outcomes</b> CMV viremia clearance, week 8 MBV 55.7% vs IAT 23.9% (p &lt;0.001)</p> <p><b>Maribavir was an effective and safe alternative treatment for refractory or resistant CMV infection post-transplant.</b></p>

## Efficacy Summary

- Maertens et al provided support for maribavir 400 mg PO BID for preemptive CMV treatment vs. higher maribavir doses and valganciclovir standard 900 mg PO BID dosing<sup>6</sup>

- The studies conducted by Papanicolaou et al and Avery et al were phase 2 and phase 3 studies that provided evidence to support the use of maribavir 400 mg PO BID for treatment of refractory or resistant CMV<sup>7,8</sup>
  - Of note, both studies reported treatment emergent resistance with maribavir with Papanicolaou et al reporting up to 13 patients developing resistance while on maribavir treatment<sup>7</sup>
- Overall, there limited evidence currently available regarding use of maribavir for CMV prophylaxis and available data is not favorable towards maribavir, so other agents such as valganciclovir or ganciclovir should be used for this indication as preferred agents
- Evidence supports use of maribavir for treatment of refractory or resistant CMV and available data suggests that if valganciclovir, ganciclovir, cidofovir, foscarnet therapy has failed or resistance to valganciclovir, ganciclovir, cidofovir, or foscarnet therapy is present, maribavir may be a viable alternative with the understanding that some treatment emergent resistance has been reported.
- Duration of therapy is dependent on response with patients receiving up to 3-12 weeks of therapy in reviewed clinical studies

## Safety Considerations

- Safety results from clinical trials as summarized in Table 2

Study	Results	Comment
Maertens (2019) <sup>6</sup> • Phase 2 study	The results reported below compare outcomes of maribavir (MBV) 400 BID to valganciclovir (VGC) 900 mg PO BID. <u>Most common treatment related side effects (MBV % vs VGC %)</u> <ul style="list-style-type: none"> <li>• Dysgeusia: <b>45%</b> vs 2%</li> <li>• Nausea: <b>22%</b> vs 15%</li> <li>• Diarrhea: <b>18%</b> vs 10%</li> <li>• Renal failure: <b>8%</b> vs 0%</li> <li>• Neutropenia: <b>2%</b> vs 5%</li> </ul>	<ul style="list-style-type: none"> <li>• MBV associated with dysgeusia</li> <li>• Neutropenia lower in MBV group than in VGC group</li> </ul>
Avery (2021) <sup>8</sup> • Phase 3 study	Common adverse events: maribavir (MBV, n=234) valganciclovir/ganciclovir (VGC, n=56), foscarnet (FOS, n=47), and cidofovir (CDV, n=6). <u>Most common treatment related side effects (MBV % vs VGC % vs FOS% vs CDV%)</u> <ul style="list-style-type: none"> <li>• Neutropenia: <b>9%</b> vs 34% vs 15% vs 0%</li> <li>• Nausea: <b>21%</b> vs 14% vs 30% vs 17%</li> <li>• Vomiting: <b>14%</b> vs 13% vs 17% vs 33%</li> <li>• Diarrhea: <b>19%</b> vs 23% vs 19% vs 17%</li> <li>• Acute kidney injury (AKI): <b>9%</b> vs 2% vs 21% vs 0%</li> </ul> <p>Discontinued trial medication due to serious adverse event MBV 13.2% vs IAT 31.9%</p>	<ul style="list-style-type: none"> <li>• Nausea, vomiting and diarrhea most common AE</li> <li>• Rates of most adverse events similar except neutropenia with VGC and AKI with foscarnet</li> <li>• More patients discontinued trial medication in the IAT arm</li> </ul>

- **Boxed warnings:** none
- **Contraindications:** none
- **Other warnings / precautions:**
  - **Risk of reduced antiviral activity when co-administered with ganciclovir or valganciclovir**
    - Maribavir antagonizes the antiviral activity of ganciclovir/valganciclovir by inhibiting human CMV pUL97 kinase, required for activation/phosphorylation of ganciclovir and valganciclovir
  - **Virologic failure during treatment and relapse post-transplant**
    - Virologic failure due to resistance and relapse during post-transplant the period (within 4 to 8 weeks after discontinuation) can occur
    - Maribavir pUL97 resistance-associated substitution confers cross-resistance to ganciclovir and valganciclovir

- Monitor CMV DNA levels and check maribavir resistance if patient is not responding to treatment
- **Risk of adverse reactions or loss of virologic response due to drug interactions**
  - Primarily metabolized by CYP3A4
  - Strong inducers can decrease maribavir plasma concentrations resulting in virologic failure
  - Maribavir has potential to increase drug concentrations of immunosuppressant drugs that are CYP3A4 and P-glycoproteins (P-gp) substrates

Drug Class: Drug Name	Effect on Concentration
<b>Anticonvulsants</b>	
Carbamazepine	↓ Maribavir
Phenobarbital	↓ Maribavir
Phenytoin	↓ Maribavir
<b>Antimycobacterials</b>	
Rifabutin	↓ Maribavir
Rifampin	↓ Maribavir
<b>Herbal Products</b>	
St. John's wort	↓ Maribavir
<b>Immunosuppressants</b>	
Cyclosporine	↑ Cyclosporine
Everolimus	↑ Everolimus
Sirolimus	↑ Sirolimus
Tacrolimus	↑ Tacrolimus

## Other Considerations

- **Pharmacokinetics**
  - Only available as oral dosage form
  - **Absorption<sup>9</sup>**
    - In humans, approximately 25% to 45% of oral maribavir absorbed
    - No data to support use for CMV of the gastro-intestinal tract with compromised gut integrity
  - **Distribution** – V<sub>ss</sub> : 27.3 L
  - **Protein Binding** – 98%, primarily to plasma albumin
  - **Metabolism** – CYP3A4 (major) and CYP1A2 (minor) to inactive metabolites
    - No dose adjustments needed for mild to moderate hepatic impairment (Child-Pugh A or B)
    - Not studied in severe hepatic impairment (Child-Pugh C)
  - **Half-Life Elimination** – Approximately 4 hours
  - **Excretion** – urine 61%, <2% unchanged; feces 14%, 5.7% unchanged
    - No dose adjustments in mild, moderate, or severe kidney impairment
    - Not studies in end-stage renal disease, including dialysis
- **Special Populations**
  - Pregnancy
    - No adequate human data are available to establish whether maribavir poses a risk to pregnancy outcomes
    - No data that it is harmful in animal studies
  - Lactation
    - It is not known whether maribavir or its metabolites are present in human or animal milk, affect milk production, or have effects on the breastfed infant
  - Geriatric Use

- No dosage adjustment is required for patients over 65 years of age based on the results from population pharmacokinetics analysis and efficacy and safety data from clinical studies
- **Acquisition issues:** Maribavir can be purchased as a wholesale transaction from Cardinal Health Specialty to be dispensed by VHA pharmacies. It does not need to be dispensed through a specialty pharmacy.

## Other Therapeutic Options

- Alternative treatments for CMV are listed in table 3 below

**Table 3 Treatment Alternatives**

Drug	Formulary status	Clinical Guidance and Efficacy	Other Considerations
<b>Maribavir (PO)</b>	TBD	<ul style="list-style-type: none"> <li>• Lacks data for use in prophylaxis</li> <li>• Alternative to preferred therapy and <b>preferred alternative</b> therapy for preemptive and treatment of CMV for patient's intolerant or refractory/resistant to preferred therapy</li> </ul>	<p>Lacks efficacy data outside of salvage therapy for refractory CMV disease</p> <p>Only available as an oral tablet</p> <p>More favorable side effect profile than preferred therapy; however, some studies with high medication discontinuation due to GI side effects</p>
<b>Valganciclovir (PO) /ganciclovir (IV)</b>	F	<ul style="list-style-type: none"> <li>• <b>Preferred</b> therapy for prophylaxis, preemptive, and treatment of CMV based on efficacy data</li> <li>• <b>First line as treatment in most situations</b></li> </ul>	<p>Carry clinically relevant risk of bone marrow suppression that makes these agents unfavorable in transplant patients with underlying bone marrow suppression at baseline</p> <p>GAN/VGC resistant CMV is not uncommon and can be a cause of failure</p>
<b>Foscarnet (IV)</b>	NF	<ul style="list-style-type: none"> <li>• <b>Alternative</b> therapy for preemptive and treatment of CMV based on efficacy and safety data</li> <li>• <b>Generally used in GAN/VGC failure or resistance</b></li> </ul>	<p>Carries clinically relevant risk of nephrotoxicity</p> <p>Only available as intravenous formulation</p> <p>May be preferred in severe illness due to long track record of use and no concern for absorption, or in less severe disease where oral absorption may be compromised</p>
<b>Cidofovir (IV)</b>	NF	<ul style="list-style-type: none"> <li>• <b>Alternative</b> therapy for preemptive and treatment of CMV based on efficacy and safety data – generally last-line due to tolerability</li> </ul>	<p>Carries clinically relevant risk of nephrotoxicity and electrolyte abnormalities</p> <p>Must be given with probenecid and fluid pre-hydration</p> <p>Only available intravenous</p>

## Projected Place in Therapy

- CMV is an opportunistic infection, affecting ~30% of all transplant patients. Prior to maribavir approval, treatment consisted of valganciclovir/ganciclovir, foscarnet, and cidofovir, which carry an unfavorable side effect profile (e.g. neutropenia, nephrotoxicity). Additionally, CMV confers resistance via UL54 and UL97 genes, which leaves limited options in cases of resistant CMV.
- Valganciclovir/ganciclovir remain the preferred therapy for prophylaxis, preemptive treatment, and treatment of CMV based on robust efficacy and safety data. However, no controlled trial data defines a best practice for selection of alternate therapy when resistance (suspected or confirmed with phenotypic tests), refractory disease (CMV viremia increase despite 2 weeks of adequate treatment, no consensus on definition), or intolerance to preferred therapy exists, such as severe neutropenia.
- Prior to maribavir, when alternative agents were indicated, foscarnet is generally required as an alternative but is limited by the need for intravenous administration, and toxicity, most notably nephrotoxicity and electrolyte abnormalities.
- Maribavir is the first in a new class of antiviral that acts on pUL97 (at different site than valganciclovir/ganciclovir) to stop CMV replication
- The primary phase 3 trial data was in refractory or resistant CMV infection and is limited to a small number of patients. Data on pre-emptive therapy is limited to a single phase 2 dose finding trial that compared it to valganciclovir. Similar CMV viremia clearance was seen, but no p values were reported.
- Phase 2 trials on the use of maribavir as prophylaxis failed to show benefit
- valganciclovir/ganciclovir is preferred over maribavir, even in most patients with bone marrow suppression given available safety and efficacy data discussed above
- Maribavir may have a role in:
  - Patients  $\geq 12$  years old post HSCT or SOT **WITH**
    - Refractory CMV infection with or without resistance to ganciclovir/valganciclovir who have failed preferred therapy
    - It may also be a treatment option in patients who cannot tolerate ganciclovir/valganciclovir, such as those with treatment limiting cytopenias, however, given existing data is limited to refractory or resistant infection, and emergence of resistance on therapy and recurrence was common, this should only be considered in select situations and in close consultations with expert in transplant and infectious diseases.
  - Foscarnet would generally be the preferred second-line therapy over maribavir in those with potentially compromised oral absorption and in those with severe / critical illness, given the long track record of use and intravenous administration
    - CMV gastrointestinal disease is one of the most common manifestations of end organ infection, and maribavir should be used cautiously, and only after careful assessment of benefit vs. risk, given the potential for reduced absorption.
    - Step-down therapy from foscarnet after improvement may also be a viable use of maribavir
    - Maribavir would also be appropriate in isolates with known or suspected resistance to foscarnet as an alternative.
  - With regards to tolerability, dysgeusia and gastro-intestinal side effects are common and often treatment limiting.
  - Maribavir is metabolized by CYP3A4 and should be used cautiously with moderate to strong CYP3A4 inducers, as no dose adjustments have been studied

## References

1. Takeda Pharmaceuticals. LIVTENCITY (maribavir) tablets, for oral use: US prescribing information. 2021. <https://content.takeda.com>. Accessed 4 April 2022.
2. Limaye AP. Ganciclovir-Resistant Cytomegalovirus in Organ Transplant Recipients. *Clin Infect Dis*. 2002;35(7):866-72.
3. Chou S, Song K, Wu J, Bo T, Crumpacker C. Drug resistance mutations and associated phenotypes detected in clinical trials of maribavir for treatment of cytomegalovirus infection [published online ahead of print, 2020 Jul 29]. *J Infect Dis*. 2020;jiaa462.
4. Marty FM, Ljungman P, Papanicolaou GA, et al. Maribavir prophylaxis for prevention of cytomegalovirus disease in recipients of allogeneic stem-cell transplants: a phase 3, double-blind, placebo-controlled, randomised trial [published correction appears in *Lancet Infect Dis*. 2011 May;11(5):343]. *Lancet Infect Dis*. 2011;11(4):284-292.
5. Winston DJ, Young JA, Pullarkat V, et al. 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;111(11):5403-5410.
6. Maertens J, Cordonnier C, Jaksch P, et al. Maribavir for Preemptive Treatment of Cytomegalovirus Reactivation. *N Engl J Med*. 2019;381(12):1136-1147.
7. 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.
8. 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.
9. Ma JD, Nafziger AN, Villano SA, Gaedigk A, Bertino JS Jr. Maribavir pharmacokinetics and the effects of multiple-dose maribavir on cytochrome P450 (CYP) 1A2, CYP 2C9, CYP 2C19, CYP 2D6, CYP 3A, N-acetyltransferase-2, and xanthine oxidase activities in healthy adults. *Antimicrob Agents Chemother*. 2006;50(4):1130-1135.
10. Azevedo LS, Pierrotti LC, Abdala E, et al. Cytomegalovirus infection in transplant recipients. *Clinics (Sao Paulo)*. 2015;70(7):515-523.
11. Kotton CN, Kumar D, Caliendo AM, et al. The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation. *Transplantation*. 2018;102(6):900-931.
12. Chemaly RF, Chou S, Einsele H, et al. Definitions of Resistant and Refractory Cytomegalovirus Infection and Disease in Transplant Recipients for Use in Clinical Trials. *Clin Infect Dis*. 2019;68(8):1420-1426.

---

Prepared June 2022. Contact person: Kelly Echevarria, National PBM Clinical Pharmacy Program Manager, Formulary management, VA Pharmacy Benefits Management Services (12PBM)

---

