Drug Monograph

Drug Name: **Livtencity™ (maribavir) tablet**
Drug Class: **Anti-Infectives: Cytomegalovirus Anti-Viral Agents**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Livtencity is available in a 200 mg tablet.
Manufacturer:	Distributed by: Takeda Pharmaceuticals America, Inc., Lexington, MA 04221.
Summary of Findings:	The Phase 3 SOLSTICE trial (Trial 303) was a multicenter, randomized, open-label, active-controlled superiority trial that evaluated the efficacy and safety of Livtencity versus investigator assigned treatment (IAT) in 352 adult hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) recipients with CMV infection that was refractory, with or without confirmed resistance, to the conventional antiviral therapies: ganciclovir, valganciclovir, foscarnet, or cidofovir. Study participants were randomized 2:1 to receive oral Livtencity (n=235) 400 mg twice daily, or IAT (n=117) for up to 8 weeks. After completion of the treatment period, study participants entered a 12-week follow-up phase. The trial met its primary endpoint, with 56% of patients who received Livtencity achieving an undetectable CMV DNA level at the end of Week 8 compared with 24% of patients who received IAT (adjusted difference: 33%; 95% CI: 23, 43; *P<0.001*) . The trial also met its key secondary endpoint of viremia clearance and control of symptoms at Week 8 with maintenance through Week 16 (adjusted difference: 9%; 95% CI: 2, 17; *P=0.013*).

Status Recommendation:	☐ Clinical Edit	☒ PA Required
	☐ Open Access	☐ PDL
Type of PA Criteria:	☒ Appropriate Indications	☐ Non-Preferred
	☐ No PA Required	☐ Preferred

©2022 Conduent Business Services, LLC All Rights Reserved.

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Cytomegalovirus (CMV) is a common type of herpes virus that is transmitted by direct contact with infectious body fluids, such as urine, saliva, blood, tears, semen, and breast milk. CMV can also be transmitted sexually and through transplanted organs and blood transfusions. The condition affects 16%–56% of SOT recipients and 30%–70% of HSCT recipients. Primary CMV infection in an organ transplant recipient can be life-threatening, affecting nearly every organ of the body, and may cause loss of the transplanted organ or death. Some common symptoms of CMV in transplant recipients can resemble the flu, but may also include pneumonia, hepatitis, encephalitis, myelitis, colitis, uveitis, retinitis, and neuropathy. Most of the time, these symptoms start between 1 and 4 months after the organ transplant. In SOT recipients, CMV infection may result in loss of the transplanted organ in up to 25% of cases. Patients who receive bone marrow, lung, heart, heart-lung, liver, pancreas-kidney, and kidney transplants require different levels of immunosuppression. Bone marrow transplant and lung transplant recipients tend to be at the highest risk for CMV infection. To treat CMV in transplant recipients, patients are generally given one or more of the following antiviral drugs: ganciclovir, valganciclovir, foscarnet, or cidofovir. However, when these standard treatments fail, the outlook for this patient population is much worse.

Dosage Form [3]

Livtencity is available in a 200 mg tablet.

Manufacturer [3]

Distributed by: Takeda Pharmaceuticals America, Inc., Lexington, MA 04221.

Indication(s) [3]

Livtencity is indicated for the treatment of adults and pediatric patients (≥12 years, weighing at least 35 kg) with post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir, or foscarnet.

Clinical Efficacy [3,4,5] (mechanism of action/pharmacology, comparative efficacy)

Livtencity is an antiviral drug against human CMV. The antiviral activity of Livtencity is mediated by competitive inhibition of the protein kinase activity of human CMV enzyme pUL97, which results in inhibition of the phosphorylation of proteins.

Pharmacokinetics:

Absorption	T_{max}: 1-3 hours
Metabolism	Hepatic

©2022 Conduent Business Services, LLC All Rights Reserved

Excretion	Renal (61%); Fecal (14%)
Half-life	4.32 hours

Clinical Trials Experience

STUDY DESIGN (NCT02931539)	Multicenter, randomized, open-label, active-controlled superiority SOLSTICE trial (Trial 303) (N=352)
INCLUSION CRITERIA	• The participant must be a recipient of hematopoietic stem cell or solid organ transplant. • The participant must have a documented CMV infection in whole blood or plasma, with a screening value of greater than or equal to (≥) 2730 international units per milliliter (IU/mL) in whole blood or ≥ 910 IU/mL in plasma in 2 consecutive assessments, separated by at least 1 day, as determined by local or central specialty laboratory quantitative polymerase chain reaction (qPCR) or comparable quantitative CMV DNA results. Both samples should be taken within 14 days prior to randomization with second sample obtained within 5 days prior to randomization. The same laboratory and same sample type (whole blood or plasma) must be used for these assessments. • The participant must have a current CMV infection that is refractory to the most recently administered of the four anti-CMV treatment agents. Refractory is defined as documented failure to achieve greater than (>) 1 log10 (common logarithm to base 10) decrease in CMV DNA level in whole blood or plasma after a 14 day or longer treatment period with intravenous (IV) ganciclovir/oral valganciclovir, IV foscarnet, or IV cidofovir. • Participants with documentation of 1 or more CMV genetic mutations associated with resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir must also meet the definition of refractory CMV infection. • The Investigator must be willing to treat the participant with at least one of the available anti-CMV drugs (ganciclovir, valganciclovir, foscarnet, or cidofovir). Note: Combination therapy with foscarnet and cidofovir is not permitted in the investigator assigned anti-CMV treatment (IAT) arm due to the potential for serious nephrotoxicity. • The participant must be ≥ 12 years of age at the time of consent. • The participant must weigh ≥ 35 kilogram (kg). • The participant must have all the following results as part of screening laboratory assessments (results from either the central laboratory or a local laboratory can be used for qualification): o Absolute neutrophil count (ANC) ≥ 1000/mm^3) (1.0 x 10^9/liter [L]) o Platelet count ≥ 25,000/mm^3 [25 x 10^9/L], o Hemoglobin ≥ 8 grams per deciliter (g/dL). o Estimated glomerular filtration rate (eGFR) > 30 (milliliters per minute (mL/min) /1.73 m^2 as assessed by Modification of Diet in Renal Disease (MDRD) formula for participants ≥ 18 years of age or Schwartz formula for participants < 18 years of age. • The participant must be willing to provide necessary samples (example [e.g.,] biopsy) for the diagnosis of tissue invasive CMV disease at baseline as determined by the Investigator. • The participant must have a life expectancy of ≥ 8 weeks.
EXCLUSION CRITERIA	• Have a current CMV infection that is considered refractory or resistant due to inadequate adherence to prior anti-CMV treatment, to the best knowledge of the Investigator. • Require ganciclovir, valganciclovir, foscarnet, or cidofovir administration for conditions other than CMV when study treatment is initiated (example:

©2022 Conduent Business Services, LLC All Rights Reserved

	herpes simplex virus (HSV) coinfection requiring use of any of these agents after the randomization) or would need a coadministration with maribavir for CMV infection. NOTE: A participant who is not continuing with the same anti-CMV drug(s) (ganciclovir, valganciclovir or foscarnet) for the study treatment (if randomized to the investigator assigned anti-CMV treatment arm), must discontinue their use before the first dose of study drug. If participant is currently being treated with cidofovir and is assigned another anti-CMV therapy by the investigator, the participant must discontinue its use at least 14 days prior to randomization at Visit 2/Day 0 and the first dose of study treatment. • Be receiving leflunomide, letermovir, or artesunate when study treatment is initiated. NOTE: Participants receiving leflunomide must discontinue the use at least 14 days prior to randomization at Visit 2/Day 0 and the first dose of study treatment. Participants receiving letermovir must discontinue use at least 3 days prior to the first dose of study treatment. Participants receiving artesunate must discontinue the use prior to the first dose of study treatment. • Have severe vomiting, diarrhea, or other severe gastrointestinal illness within 24 hours prior to the first dose of study treatment that would preclude administration of oral/enteral medication. • Have known hypersensitivity to the active substance or to an excipient for a study treatment. • Have tissue invasive CMV disease with central nervous system involvement including the retina (example, CMV retinitis). • Have serum aspartate aminotransferase (AST) > 5 times upper limit of normal (ULN) at screening, or serum alanine aminotransferase (ALT) > 5 times ULN at screening, or total bilirubin ≥ 3.0 x ULN at screening (except for documented Gilbert's syndrome), by local or central lab. Participants with biopsy confirmed CMV hepatitis will not be excluded from study participation despite AST or ALT > 5 times ULN at screening. • Have known positive results for human immunodeficiency virus (HIV). Participants must have a confirmed negative HIV test result within 3 months of study entry or, if unavailable, be tested by a local laboratory during the screening period. • Require mechanical ventilation or vasopressors for hemodynamic support at the time of enrollment. • Be female and pregnant or breast feeding. • Have previously received maribavir. • Have received any investigational agent with known anti-CMV activity within 30 days before initiation of study treatment or investigational CMV vaccine at any time. • Have active malignancy except for nonmelanoma skin cancer. Participants who have had a hematopoietic stem cell transplant (HSCT) and who experience relapse or progression of the malignancy as per investigator's opinion are not to be enrolled. • Be undergoing treatment for acute or chronic hepatitis C.

TREATMENT REGIMEN	Participants were randomized 2:1 to receive one of the following for up to 8 weeks:
	• Livtencity (n=235) 400 mg, twice daily or
	• IAT (n=117), including:
	  ○ Foscarnet (41%)
	  ○ Ganciclovir (24%)
	  ○ Valganciclovir (24%)
	  ○ Cidofovir (5%)
	  ○ Foscarnet plus Valganciclovir (3%)

©2022 Conduent Business Services, LLC All Rights Reserved

<table>
<tr><td></td><td>
Foscarnet plus Ganciclovir (3%)
The mean treatment durations (SD) for Livtencity and IAT were 48.6 (±13.82) and 31.2 (±16.91) days, respectively.
</td></tr>
<tr><td>RESULTS</td><td>
The primary efficacy endpoint was confirmed CMV DNA level <LLOQ (i.e., <137 IU/mL) as assessed by Cobas AmpliPrep/Cpbas TaqMan CMV test) at the end of Week 8.
<table>
<tr><th></th><th>Livtencity
400 mg Twice Daily
N=235
n (%)</th><th>IAT
N=117
n (%)</th></tr>
<tr><td>Primary Endpoint: Confirmed CMV DNA Level <LLOQ at Week 8[a]</td><td></td><td></td></tr>
<tr><td>Responders</td><td>131 (56)</td><td>28 (24)</td></tr>
<tr><td>Adjusted Difference in Proportion of Responders (95% CI)[b]</td><td>33 (23, 43)</td><td></td></tr>
<tr><td>p-value: Adjusted[b]</td><td><0.001</td><td></td></tr>
</table>
[a] Confirmed CMV DNA level < LLOQ at the end of Week 8 (2 consecutive samples separated by at least 5 days with DNA levels <LLOQ [i.e., <137 IU/mL]).
[b] Cochran-Mantel-Haenszel weighted average approach was used for the adjusted difference in proportion (maribavir – IAT), the corresponding 95% CI, and the p-value after adjusting for the transplant type and baseline plasma CMV DNA concentration. Only those with both stratification factors were included in the computation.

The key secondary endpoint was CMV DNA level <LLOQ and CMV infection symptom control at the end of Study Week 8 with maintenance of the treatment effect through Week 16.
<table>
<tr><th></th><th>Livtencity
400 mg Twice Daily
N=235
n (%)</th><th>IAT

N=117
n (%)</th></tr>
<tr><td>Secondary endpoint: Achievement of CMV DNA Level <LLOQ and Symptom Control[a] at Week 8 with Maintenance Through Week 16</td><td></td><td></td></tr>
<tr><td>Responders</td><td>44 (19)</td><td>12 (10)</td></tr>
<tr><td>Adjusted Difference in Proportion of Responders (95% CI)[b]</td><td>9 (2,17)</td><td></td></tr>
<tr><td>p-value: Adjusted[b]</td><td>0.013</td><td></td></tr>
</table>
[a] CMV infection symptom control was defined as resolution or improvement of tissue-invasive disease or CMV syndrome for symptomatic patients at baseline, or no new symptoms for patients who were asymptomatic at baseline.
[b] Cochran-Mantel-Haenszel weighted average approach was used for the adjusted difference in proportion (maribavir – IAT), the corresponding 95% CI, and the p-value after adjusting for the transplant type and baseline plasma CMV DNA concentration. Only those with both stratification factors were included in the computation.

Although Livtencity had similar efficacy across stratified subpopulations, it was noted to be less effective in patients with CMV DNA levels ≥50,000 IU/mL and in patients without genotypic resistance.
After the end of treatment phase, 65/131 (50%) of patients in the Livtencity group and 11/28 (39%) patients in the IAT group who achieved CMV DNA level <LLOQ experienced virologic relapse during the follow-up period. In both groups, most of the relapses occurred within 4 weeks after study drug discontinuation. Six percent of patients in both groups developed new-onset symptomatic CMV infection during the entire study .

</td></tr>
<tr><td>SAFETY</td><td>Discussed in the Adverse Effects section below.</td></tr>
</table>

Abbreviations: AE=adverse event; CI=confidence interval; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; HSCT=hematopoietic stem cell transplant; IAT=investigator assigned anti-CMV treatment; LLOQ=lower limit of quantification; N=number of patients; SOT=solid organ transplant.

©2022 Conduent Business Services, LLC All Rights Reserved

Contraindications (3,4)

- None

Warnings and Precautions (3,4)

- Livtencity may antagonize the antiviral activity of ganciclovir and valganciclovir. Coadministration is not recommended.
- Virologic failure can occur during and after treatment with Livtencity. Monitor CMV DNA levels and check for resistance if patient does not respond to treatment. Some Livtencity pUL97 resistance-associated substitutions confer cross-resistance to ganciclovir and valganciclovir.
- The concomitant use of Livtencity and certain drugs may result in potentially significant drug interactions, some of which may lead to reduced therapeutic effect of Livtencity or adverse reactions of concomitant drugs (*See Drug Interactions section below*).
- Livtencity has the potential to increase the drug concentrations of immunosuppressant drugs that are CYP3A4 and/or P-gp substrates where minimal concentration changes may lead to serious adverse events (including tacrolimus, cyclosporine, sirolimus, and everolimus). Frequently monitor immunosuppressant drug levels throughout treatment with Livtencity, especially following initiation and after discontinuation of Livtencity and adjust the dose, as needed.
-

Adverse Effects (3,4)

Most common, >10%	Livtencity N=234 %	Investigator-Assigned Treatment[a] N=116 %
Taste disturbance[b]	46	4
Nausea	21	22
Diarrhea	19	21
Vomiting	14	16
Fatigue	12	9

[a] IAT (Investigator Assigned Treatment) included monotherapy or dual therapy with ganciclovir, valganciclovir, foscarnet, or cidofovir as dosed by the investigator
[b] Taste disturbance includes the following reported preferred terms: ageusia, dysgeusia, hypogeusia and taste disorder

Drug Interactions (3,4)

Established and Other Potentially Significant Drug Interactions[a]

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comments
Antiarrhythmics		
Digoxin	↑ Digoxin	Use caution when Livtencity and digoxin are coadministered. Monitor serum digoxin concentrations. The dose of digoxin may need to be reduced when coadministered with Livtencity[c]
Anticonvulsants		
Carbamazepine	↓ Maribavir	A dose adjustment of Livtencity to 800 mg twice daily is recommended when co-administered with carbamazepine.
Phenobarbital	↓ Maribavir	A dose adjustment of Livtencity to 1,200 mg twice daily is recommended when co-administration with phenobarbital.
Phenytoin	↓ Maribavir	A dose adjustment of Livtencity to 1,200 mg twice daily is recommended when co-administration with phenytoin.
Antimycobacterials		

©2022 Conduent Business Services, LLC All Rights Reserved

Rifabutin	↓ Maribavir	Co-administration of Livtencity and rifabutin is not recommended due to potential for a decrease in efficacy of Livtencity.
Rifampin	↓ Maribavir	Co-administration of Livtencity and rifampin is not recommended due to potential for a decrease in efficacy of Livtencity.
Herbal Products		
St. John's Wort	↓ Maribavir	Co-administration of Livtencity and St. John's wort is not recommended due to potential for a decrease in efficacy of Livtencity.
HMG-CoA Reductase Inhibitors		
Rosuvastatin	↑ Rosuvastatin	The patient should be closely monitored for rosuvastatin-related events, especially the occurrence of myopathy and rhabdomyolysis[c]
Immunosuppressants		
Cyclosporine	↑ Cyclosporine	Frequently monitor cyclosporine levels throughout treatment with Livtencity, especially following initiation and after discontinuation of Livtencity and adjust dose, as needed[c] .
Everolimus	↑ Everolimus	Frequently monitor everolimus levels throughout treatment with Livtencity, especially following initiation and after discontinuation of Livtencity and adjust dose, as needed[c] .
Sirolimus	↑ Sirolimus	Frequently monitor sirolimus levels throughout treatment with Livtencity, especially following initiation and after discontinuation of Livtencity and adjust dose, as needed[c] .
Tacrolimus	↑ Tacrolimus	Frequently monitor tacrolimus levels throughout treatment with Livtencity, especially following initiation and after discontinuation of Livtencity and adjust dose, as needed[c] .

↓=decrease, ↑=increase
[a] This table is not all inclusive.
[b] The interaction between LIVTENCITY and the concomitant drug was evaluated in a clinical study.
[c] Refer to the respective prescribing information.

Dosage and Administration (3,4)

The recommended dosage in adults and pediatric patients (12 years of age and older and weighing at least 35 kg) is 400 mg (two 200 mg tablets) taken orally twice daily with or without food.
If Livtencity is co-administered with carbamazepine, increase the dosage of Livtencity to 800 mg twice daily.
If Livtencity is co-administered with phenytoin or phenobarbital, increase the dosage of Livtencity to 1,200 mg twice daily.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/Month
Maribavir	Livtencity™	Takeda Pharmaceuticals USA	400 mg orally twice daily with or without food	$24,900

** Wholesale Acquisition Cost

Conclusion

Livtencity is a cytomegalovirus (CMV) pUL97 kinase inhibitor indicated for the treatment of adults and pediatric patients (≥12 years and weighing at least 35 kg) with post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir or foscarnet. In the Phase 3 SOLSTICE trial, Livtencity

©2022 Conduent Business Services, LLC All Rights Reserved

achieved viremia clearance in 56% of patients compared with 24% of patients receiving traditional treatment. The trial also met its key secondary endpoint of viremia clearance and control of symptoms at Week 8 with maintenance through Week 16. The most common adverse events in patients treated with Livtencity were taste disturbance, nausea, diarrhea, vomiting, and fatigue. Although Livtencity had similar efficacy across stratified subpopulations, it was noted to be less effective in patients with CMV DNA levels ≥50,000 IU/mL and in patients without genotypic resistance. Livtencity will initially be used to treat resistant CMV disease in organ transplant recipients; however, Takeda is investigating Livtencity in an ongoing Phase 3 clinical trial as a first-line treatment for CMV in HSCT recipients.

Recommendation

The MO HealthNet Division recommends prior authorization status for this product.

References

1) IPD Analytics: New Drug Review: Livtencity (maribavir). Accessed February 13, 2022.
2) Centers for Disease Control and Prevention. Cytomegalovirus (CMV) and Congenital CMV Infection: Clinical Overview. https://www.cdc.gov/cmv/clinical/overview.html. Accessed February 13, 2022.
3) Livtencity (maribavir) [prescribing information]. Lexington, MA: Takeda Pharmaceuticals America, Inc.; November 2021.
4) U.S. National Library of Medicine. Efficacy and Safety of Maribavir Treatment Compared to Investigator-Assigned Treatment in Transplant Recipients with Cytomegalovirus (CMV) Infections That Are Refractory or Resistant to Treatment with Ganciclovir, Valganciclovir, Foscarnet, or Cidofovir. https://clinicaltrials.gov/ct2/show/NCT02931539?term=NCT02931539&draw=2&rank=1. Accessed February 13, 2022.
5) Clinical Pharmacology [Drug Reference Database]. https://www.clinicalkey.com/. Accessed February 13, 2022.

Prepared by: April Ash, PharmD
Date: February 13, 2022

©2022 Conduent Business Services, LLC All Rights Reserved