NEW DRUG APPROVAL

Brand Name	Livtencity™
Generic Name	maribavir
Drug Manufacturer	Takeda Pharmaceuticals America, Inc

New Drug Approval

FDA Approval Date: November 23, 2021
Review Designation: Priority; Orphan
Type of Review: Type 1 - New Molecular Entity; New Drug Application (NDA): 215596
Dispensing Restrictions: Specialty Only, Limited Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Cytomegalovirus (CMV) is a ubiquitous virus that commonly infects people of all ages throughout the world. The spectrum of human illness caused by cytomegalovirus (CMV) is diverse and mostly dependent on the host. CMV infections in immunocompromised patients cause substantial morbidity and mortality, especially among transplant recipients and those infected with the human immunodeficiency virus (HIV). Infection in the immunocompetent host is generally asymptomatic or may present as a mononucleosis syndrome. However, occasionally, primary CMV infection can lead to severe organ-specific complications with significant morbidity and mortality. Infection of pregnant women, even if asymptomatic, is occasionally associated with the syndrome of congenital CMV in new-borns.

The Centers for Disease Control and Prevention (CDC) estimates that nearly 1 in 3 children in the United States have been exposed to the virus by 5 years of age, and more than half of the U.S. population has been exposed to the virus by 40 years of age. Most people are asymptomatic; however, in immunosuppressed populations, CMV disease can be life-threatening. In solid organ transplant (SOT) recipients, CMV infection may result in loss of the transplanted organ in up to 25% of cases.

Efficacy

The efficacy of Livtencity was based on results of the Phase 3 SOLSTICE trial, in which Livtencity met its primary endpoint of superiority in CMV viremia clearance compared with conventional antiviral therapies (ganciclovir, valganciclovir, cidofovir, or foscarnet) in 352 transplant recipients with refractory CMV infections (with or without genotypic resistance). The overall safety of Livtencity appears comparable to or better than the conventional CMV antivirals.

Table 1. SOLSTICE (NCT02931539; Trial 303): Study Design and Results Summary	
Study Population (N = 352)	• Participants were HSCT and SOT adult recipients with CMV infection refractory, with or without or resistance, to conventional antiviral therapies including ganciclovir, valganciclovir, foscarnet, or cidofovir. • Patients with CMV infection involving the central nervous system, including the retina, were excluded from the trial. • Mean age: 53 years (range, 18–79 years) • 61% male • 76% White • 83% not Hispanic/Latino

Interventions	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%)
	  ○ 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.

Endpoints	• **Primary efficacy endpoint:** confirmed CMV DNA level <LLOQ (i.e. <137 IU/mL) as assessed by Cobas AmpliPrep/Cobas TaqMan CMV test) at the end of Week 8. • **Key secondary endpoint:** 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.
Efficacy Results	• **Primary**: CMV DNA level <LLOQ was achieved by 131 (56%) patients who received Livtencity vs. 28 (24%) of patients in the IAT group at Week 8 (adjusted difference: 33%; 95% CI: 23–43; *P* <0.001). • **Secondary**: CMV DNA level <LLOQ and symptom control at Week 8 with maintenance through Week 16 was achieved in 44 (19%) of patients who received Livtencity vs. 12 (10%) of patients in the IAT group (adjusted difference: 9%; 95% CI: 2–17; *P* = 0.013) • 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 period.

Safety

ADVERSE EVENTS

The most common adverse events (all grades, >10%) in subjects treated with Livtencity™ were taste disturbance, nausea, diarrhea, vomiting, and fatigue.

WARNINGS & PRECAUTIONS

- 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 maribavir 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.
- 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.

CONTRAINDICATIONS

None.

Clinical Pharmacology

MECHANISMS OF ACTION

Maribavir is an antiviral drug against human cytomegalovirus (CMV). Pharmacological activity is due to the parent drug. The antiviral activity is mediated by competitive inhibition of the protein kinase activity of human CMV enzyme pUL97, which results in inhibition of the phosphorylation of proteins. Maribavir inhibited wild type pUL97 protein kinase in a biochemical assay with an IC_{50} value of 0.003 microM. Maribavir and its 5'-mono- and 5'-triphosphate derivatives at 100 microM had no significant effect on the incorporation of deoxynucleoside triphosphates (dNTPs) by human CMV DNA polymerase. At a concentration of 100 microM, neither maribavir nor its 5'-triphosphate derivative inhibited CMV DNA polymerase delta; however, the 5'-monophosphate derivative inhibited incorporation by polymerase delta of all 4 natural dNTPs by approximately 55%.

Dose & Administration

ADULTS

400 mg (two 200 mg tablets) orally twice daily with or without food.

PEDIATRICS

Cytomegalovirus, refractory, treatment (posttransplant): Children ≥12 years and Adolescents weighing ≥35 kg: Oral: 400 mg twice daily.

Dosage adjustment for concomitant therapy: Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

No dosage adjustment is needed for mild, moderate, or severe renal impairment. Administration in patients with end stage renal disease (ESRD), including patients on dialysis, has not been studied.

HEPATIC IMPAIRMENT

No dosage adjustment is needed for mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Administration in patients with severe hepatic impairment has not been studied.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 200 mg of maribavir.