Maribavir (Livtencity™) New Drug Update

December 2021

Nonproprietary Name	maribavir
Brand Name	Livtencity
Manufacturer	Takeda
Form	Oral tablet
Strength	200 mg
FDA Approval	November 23, 2021
Market Availability	Available
FDA Approval Classification	Breakthrough Therapy, Orphan Drug, Priority Review
FDB Classification- Specific Therapeutic Class (HIC3)	Antivirals, General (W5A)

INDICATION[1]

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

PHARMACOKINETICS

With time-independent pharmacokinetics and following a single oral dose of 50 mg to 1,600 mg (0.125 to 4 times the recommended dose) and multiple doses up to 2,400 mg per day (3 times the recommended daily dose), maribavir plasma exposure increased approximately dose-proportionally. Steady state is reached within 2 days with twice-daily dosing regimen and with mean accumulation ratios of C_{max} and AUC ranging from 1.37 to 1.47. The median time to maximum plasma concentration (T_{max}) is 1 to 3 hours. The mean apparent steady-state volume of distribution (V_{ss}) is 27.3 liters (L). The maximum concentration (C_{max}) is 17.2 mcg/mL (39.3% coefficient of variation [CV]) and the area under the time concentration curve over a dosing interval ($AUC_{0\text{-}tau}$) is 128 ug*h/mL (50.7% CV), and the concentration at the end of a dosing interval (C_{tau}) is 4.9 mcg/mL with 89.7% CV. Maribavir is 98% bound to human plasma proteins across the concentration range of 0.05 to 200 mcg/mL with a blood-to-plasma ratio of 1.37. The mean elimination half-life ($t_{1/2}$) in transplant patients is 4.32 hours, and the mean oral clearance is 2.85 L/hours. Maribavir is primarily eliminated via hepatic metabolism cytochrome P450 pathways (CYP) 3A4 (major) and CYP1A2 (minor). Maribavir is excreted 61% in the urine (< 2% unchanged) and 14% in the feces (5.7% unchanged) following a single radiolabeled 400 mg dose of maribavir oral solution containing 200 nCi of total radioactivity.

CONTRAINDICATIONS/WARNINGS

There are no known contraindications to the use of maribavir.

Coadministration of maribavir with ganciclovir and valganciclovir may reduce antiviral activity of ganciclovir and valganciclovir; therefore, coadministration is not recommended.

Maribavir may cause virologic failure due to resistance during and after treatment with maribavir. Maribavir may cause virologic relapse during posttreatment period, within 4 to 8 weeks after therapy discontinuation. Maribavir pUL97 resistance-associated substitutions can confer cross-resistance to ganciclovir and valganciclovir; therefore, monitoring of CMV deoxyribonucleic acid (DNA) levels and maribavir resistance is recommended if there is non-response or relapses.

Drug interactions with maribavir may result in risk of adverse reactions of concurrent drug or loss of virologic response to maribavir and therefore should be monitored.

DRUG INTERACTIONS

Strong CYP3A4 inducers decrease plasma concentrations of maribavir and may result in reduced virologic response, therefore coadministration is not recommended, except for selected anticonvulsants.

With immunosuppressants that are CYP3A4 and/or P-glycoprotein (P-gp) substrates, where minimal concentration changes may lead to serious adverse events, drug levels should be frequently monitored throughout treatment with maribavir, especially after initiation and discontinuation of maribavir; adjust the immunosuppressant dose, if needed.

As maribavir is a weak CYP3A4 inhibitor as well as a P-gp and BCRP inhibitor, concurrent use with sensitive substrates of CYP3A, P-gp and BCRP may lead to clinically important increase in plasma levels of these substrates. Potentially significant drug interactions may occur when coadministered with other agents such as digoxin, anticonvulsants, antimycobacterials, herbal products, HMG-CoA reductase inhibitors, and immunosuppressants. Digoxin concentrations can be increased when coadministered with maribavir; use caution and monitor serum digoxin levels as the dose of digoxin may need to be decreased. Maribavir concentration may be reduced when coadministered with anticonvulsants (e.g., carbamazepine, phenobarbital, phenytoin) and dose adjustments of maribavir are recommended with these anticonvulsants. Maribavir concentration may be reduced when administered with antimycobacterials (e.g., rifabutin, rifampin) and coadministration is not recommended due to potential decrease in efficacy of maribavir. Maribavir concentration may also be reduced with St. John's wort and coadministration is not recommended due to potential decrease in maribavir efficacy. Maribavir may increase rosuvastatin drug concentration and cause rosuvastatin related adverse events (e.g., myopathy, rhabdomyolysis) which should be closely monitored. Maribavir has the potential to increase drug concentrations of immunosuppressant drugs (e.g., tacrolimus, cyclosporine, sirolimus, everolimus) and drug levels of these agents should be frequently monitored throughout treatment, especially following initiation and after discontinuation of maribavir, dose adjustment may be needed.

COMMON ADVERSE EFFECTS

The most common adverse effects reported in patients treated with maribavir (>10%) all grades, compared to investigator-assigned treatment (IAT) (e.g., ganciclovir, valganciclovir, cidofovir, foscarnet), included taste disturbance (46% versus 4%), nausea (21% versus 22%), diarrhea (19% versus 21%),

vomiting (14% versus 16%), and fatigue (12% versus 9%). A similar incidence of serious adverse effects occurred in maribavir (38%) group compared to IAT (37%) group which included Infections and Infestations System Organ Class (SOC) with CMV infection/disease being the most common is each group. More patients in the IAT group (32%) discontinued therapy due to adverse effects compared to maribavir group (13%) and most were due to neutropenia (9%) and acute kidney injury (5%) in the IAT group. The most common laboratory abnormalities (> 20%) were hemoglobin (≥ 8 to < 9.5 g/dL, 32% versus 28%) for maribavir versus IAT, respectively, and creatinine (> 1.5 to ≤ 2.5 mg/dL, 33% versus 25%, respectively).

SPECIAL POPULATIONS

Pregnancy

There are no data regarding use of maribavir during human pregnancy; however, embryo-fetal survival was reduced in animal studies. Data for maribavir in pregnancy are inadequate to advise of maternal or fetal risk.

Pediatrics

The safety and efficacy of maribavir was established in pediatric patients ≥ 12 years of age and weighing ≥ 35 kg based on controlled studies in adults, population pharmacokinetic modeling, and disease course similarity to adults. The safety and efficacy of maribavir have not been established in pediatric patients ages < 12 years of age and < 35 kg.

Geriatrics

In a clinical trial, no differences in pharmacokinetics, safety, or efficacy were detected in patients ≥ 65 years of age compared to younger patients.

Hepatic Impairment

No dosage adjustment of maribavir is needed in patients with mild (Child-Pugh Class A) to moderate (Child-Pugh Class B) hepatic impairment; the impact of severe (Child-Pugh Class C) hepatic impairment on maribavir has not been determined.

Renal Impairment

No dosage adjustment of maribavir is needed in patients with mild to severe renal impairment (creatinine clearance range, 12 to 70 mL/minute); the impact of end stage renal disease (ESRD), including dialysis, on maribavir's safety and effectiveness has not been determined.

DOSAGES

The recommended dose of maribavir is 400 mg orally twice daily with or without food.

If coadministered with carbamazepine, the dosage of maribavir should be increased to 800 mg twice daily. If coadministered with phenytoin or phenobarbital, the dosage of maribavir should be increased to 1,200 mg twice daily.

CLINICAL TRIALS[2,3,4]

A literature search was performed using "maribavir", "post-transplant", and "cytomegalovirus (CMV)."

A global, multicenter, randomized 2:1, open-label, active-controlled superiority phase 3 study (SOLSTICE; NCT02931539) evaluated the efficacy and safety of maribavir in 352 patients (≥ 12 years of age and weigh ≥ 35 kg) post-transplant (hematopoietic stem cell transplant [HSCT] or solid organ transplant [SOT]) recipients with CMV infection refractory to ≥ 1 of the conventional antiviral therapies that were investigator-assigned (e.g., ganciclovir, valganciclovir, foscarnet, or cidofovir). Patients were randomized to receive either maribavir 400 mg orally twice daily or IAT (dosed by the investigator) for up to 8 weeks following a refractory diagnosis; this was then followed by a 12-week follow-up phase. Patients were included if they were a recipient of HSCT or SOT, documented CMV infection, refractory to the most recently administered anti-CMV treatment, and met baseline laboratory screening qualifications. Patients were excluded if they had CMV involving the central nervous system, including the retina. The mean age was 53 years, and the majority were male (61%), Caucasian (76%), and not Hispanic or Latino (83%). Foscarnet was the most common IAT used in 41% of patients, ganciclovir and valganciclovir (24% each), and cidofovir in 6 subjects. Combination therapy was also used in 4 subjects (foscarnet and valganciclovir), and 3 subjects (foscarnet and ganciclovir). The majority of patients in each group (maribavir versus IAT, respectively) received SOT (60% versus 59%) and most were kidney transplants (52% versus 46%, respectively). CMV DNA levels were low (< 9,100 IU/mL) in most patients (65% versus 73%, respectively). The majority of patients did not have a confirmed symptomatic CMV infection at baseline (91% versus 93%, respectively).

The primary endpoint was confirmed CMV DNA level < the lower limit of quantification (LLOQ) (< 137 IU/mL) as assessed by an approved test (e.g., COBAS® AmpliPrep/COBAS® TaqMan® CMV test) at the end of week 8. The primary endpoint for maribavir was superior to IAT (56% versus 24%, respectively; difference, 32.8%; 95% confidence interval [CI], 22.8 to 42.74; p<0.001). The majority of non-responders were due to virologic failure (CMV DNA never < LLOQ or breakthrough) in the maribavir group (maribavir 34% versus IAT 36%); however, most non-responders in the IAT group were due to drug/study discontinuation (38%) compared with 9% for maribavir. Although the treatment effect of maribavir was generally similar for transplant type, patient age, and presence of CMV syndrome/disease at baseline, maribavir was less effective in those with increased CMV DNA levels (≥ 50,000 IU/mL) and those with absence of genotypic resistance. The main secondary endpoint was CMV DNA level < LLOQ and CMV infection symptom control at the end of week 8 that was maintained through week 16. The proportion of responders for this endpoint was 19% in the maribavir arm compared with 10% in IAT (adjusted p-value=0.013). Following the treatment phase, 50% of patients in the maribavir arm and 39% of patients in the IAT group who had reached CMV DNA level < LLOQ had a virologic relapse with the majority of the relapses 89% in maribavir arm and all in IAT arm occurring within 4 weeks of study drug discontinuation (median time to relapse, 15 days; range, 7 to 71 versus 15 days; range, 7 to 29, respectively). During the entire study, 6% of patients in each arm developed new onset symptomatic CMV infection. All-cause mortality occurred at similar percentages of subjects in each group (11%).

OTHER DRUGS USED FOR CONDITION[5,6]

The 2019 American Society of Transplantation Infectious Diseases Community of Practice guidelines for solid organ transplant recipients recommend valganciclovir and intravenous (IV) ganciclovir as the drugs of choice in CMV management, and the mainstays of CMV prevention are antiviral prophylaxis and preemptive therapy. Foscarnet and cidofovir, due to risk of nephrotoxicity, are considered second-line and third-line alternative agents, respectively. Most transplant centers prefer pre-emptive approach for hematopoietic cell transplant (HCT) recipients where therapy is initiated after CMV viremia is detected in asymptomatic patients rather than the CMV prophylaxis approach; in addition, weekly quantitative CMV testing is recommended. Pre-emptive regimens are recommended to start in the posttransplant period and are continued for a minimum of 2 weeks with weekly polymerase chain reaction (PCR) monitoring. Refractory and resistant CMV occurs after at least 2 weeks of an appropriate antiviral regimen and CMV DNA increases (e.g., > 1 log10 increase between baseline value and viral load at ≥ 2 weeks). Selection of conventional therapy, monotherapy or combination therapy, includes ganciclovir, valganciclovir, cidofovir, or foscarnet, and is based on donor and recipient CMV serotype combination and the kidney function. Foscarnet is recommended as the first-line drug of choice in treatment of UL97-mutant ganciclovir-resistant CMV. In high-risk HCT patients, CMV prophylaxis is recommended.

PLACE IN THERAPY[7,8,9,10,11]

Cytomegalovirus (CMV) is a beta herpesvirus that commonly infects humans and typically resides latent and asymptomatic in the body but may reactivate during periods of immunosuppression. CMV is one of the most common and serious life-threatening opportunistic infections occurring post-transplant. Post-transplant CMV infection occurs in solid organ transplant recipients (16% to 56%) and hematopoietic stem cell transplant recipients (30% to 70%). Following the transplant, CMV infection can be acquired or reactivated and lead to serious complications including loss of the transplanted organ and failure of the graft, or loss of life. Low rates of developing a resistance mutation to antiviral treatment have been reported in a clinical trial of SOT recipients: ganciclovir (2.3%) and valganciclovir (3.6%).

Maribavir (Livtencity) is the first and only treatment approved for post-transplant CMV infection that is resistant to conventional antiviral treatment without regard to genotype resistance. More than twice the proportion of patients with refractory CMV infection treated with maribavir had confirmed CMV DNA level below what was measurable (LLOQ < 137 IU/mL) at the end of week 8 (treatment phase) compared to conventional antiviral treatment (IAT). Maribavir is an antiviral drug against human CMV that is orally bioavailable. It acts to inhibit CMV replication, encapsidation, and nuclear egress by targeting the CMV enzyme pUL97, thus acting as pUL97 protein kinase inhibitor. Maribavir was statistically superior to conventional antiviral therapy in achieving confirmed clearance of plasma CMV DNA at the end of the treatment period (week 8). Taste disturbance occurred in patients taking maribavir (46%) and most cases resolved (37%) while on therapy with a median duration of 43 days (range, 7 to 59 days). Maribavir is expected to be used for the indicated population of patients with post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir, or foscarnet.

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	N/A
Clinical Edit	**Initial Approval Criteria** ▪ Patient is ≥ 12 years of age; **AND** ▪ Patient must weigh ≥ 35 kilogram (kg); **AND** ▪ Patient is a recipient of a hematopoietic stem cell or solid organ transplant; **AND** ▪ Patient has documented cytomegalovirus (CMV) infection in whole blood or plasma (screening value ≥ 2,730 IU/mL in whole blood or ≥ 910 IU/mL in plasma) in 2 consecutive assessments separated by ≥ 1 day; **AND** ▪ Patient has current CMV infection that is refractory (documented failure to achieve > 1 log10 decrease in CMV deoxyribonucleic acid [DNA] level in whole blood or plasma after ≥ 14 days treatment) to anti-CMV treatment agents (ganciclovir, valganciclovir, cidofovir, or foscarnet), even with documented genetic mutations associated with resistance; **AND** ▪ Maribavir will NOT be coadministered with ganciclovir or valganciclovir; **AND** ▪ Patient will be monitored for clinically important drug interactions that could result in decreased therapeutic effect of maribavir. **Renewal Criteria** ▪ Patient must continue to meet the above criteria; **AND** ▪ Patient must have disease improvement and/or stabilization OR improvement in the slope of decline (> 1 log10 decrease in CMV DNA level in whole blood or plasma after 14 days or longer treatment); **AND** ▪ Patient has NOT experienced any treatment-restricting adverse effects (e.g., dysgeusia, diarrhea, nausea, and recurrence of underlying disease); **AND** ▪ Patient is NOT a non-responder (resistant) to maribavir.
Quantity Limit	120 tablets per 30 days (800 mg daily) With carbamazepine: 240 tablets per 30 days (1,600 mg daily) With phenytoin or phenobarbital: 360 tablets per 30 days (2,400 mg daily)
Duration of Approval	Initial: 6 months Renewal: 6 months
Drug to Disease Hard Edit	None

REFERENCES

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