maribavir

NDA 215596 **43 entries** HI Study Food-Effect Study approval year: 2021

Therapeutic class	Anti-Infective Agents ⟶ Antivirals
Brand name	LIVTENCITY (tablets)
Indications and usage	LIVTENCITY is a cytomegalovirus (CMV) pUL97 kinase inhibitor indicated for the treatment of adults and pediatric patients (12 years of age and older 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.
Clinical recommended dosage	400 mg orally twice daily with or without food
Molecular weight	376.24 g/mol
Biopharmaceutics class	Class II: High permeability - Low solubility reference: NDA# 215596 Product Quality Review(s)

Characteristics

CYP2C19 weak inhibitor

CYP3A weak inhibitor

P-gp clinical inhibitor

Pharmacokinetic profile

Accumulation ratio	1.37-1.47; steady state is reached within 2 days
B/P	1.37 ± 0.13 (0.005-10 µg/mL)
Biopharmaceutics class	Class II: High permeability - Low solubility
C_{max}	45.72 µmol/L 17.2 (39.3%) µg/mL 400 mg orally twice daily in transplant patients with CMV
Clearance	2.85 L/h (transplant patients with CMV); 0.051 L/h (CLrenal)
Clinical recommended dosage	400 mg orally twice daily with or without food
Dose proportionality	yes - Cmax and AUC increase approximately dose-proportionally at single doses of 50-1600 mg and at multiple doses up to 2400 mg/day; PK is time-independent
Elimination pathway	extensive metabolism
F_a	0.90
F_e	< 0.02 (oral)
F_m *in vitro*	0.664 (CYP3A4), 0.336 (CYP1A2) - based on recombinant CYPs

F_m *in vivo*	0.35 (CYP3A4) - also a substrate of P-gp, this value back-calculated from the maximum AUCR with ketoconazole may overestimate fm as ketoconazole also inhibits P-gp
F_u *in vitro*	0.73 (fu,mic)
k_a	1.2 /h
logP	2.86 at pH 7.4
Molecular weight	376.24 g/mol
Permeability	5.6 x 10^-6 cm/sec (Papp in Caco-2 cells)
pKa	5.2
Plasma protein binding	98% (0.05-200 µg/mL)
Solubility (at different pH)	pH-dependent solubility: soluble at pH < 3.0, 0.57-1.49 mg/mL at pH > 3.9
$T_{1/2}$	4.32 h (transplant patients with CMV)
T_{max}	1.0-3.0 h
Vd	27.3 L
Comments	Based on in vivo clearance and in vitro data, the fm values of CYP3A4, CYP1A2, and UGTs were estimated to be 0.35, 0.04, and 0.61.
References	LIVTENCITY Product Label; NDA# 215592 Integrated Review, Product Quality Review(s); PMID# 18316526

DDI summary

Last edited 1/27/2022

NDA 215596 **43 entries** **HI Study** **Food-Effect Study** approval year: 2021

DDI risk level as object **II (Intermediate)**

DDI risk level as precipitant **III (No or Low)**

Key Highlights

Maribavir (LIVTENCITY; oral tablet) is a cytomegalovirus (CMV) pUL97 kinase inhibitor indicated for the treatment of adults and pediatric patients (12 years of age and older 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. The recommended dose is 400 mg orally twice daily with or without food (LIVTENCITY Product Label).

In vitro studies suggest that maribavir is primarily metabolized by CYP3A4. In vivo, concomitant administration with ketoconazole, a strong CYP3A4 inhibitor, increased maribavir AUC 1.53-fold. Based on PBPK modeling and simulations, co-administration with erythromycin, a moderate CYP3A4 inhibitors, was predicted to increase maribavir AUC 1.40-fold. However, these changes are not considered to be clinically significant.

Maribavir is sensitive to induction. Co-administration of maribavir with rifampin, a strong CYP3A4 inducer, decreased maribavir AUC by 60% and Cmin by 82%. According to the Product Label, co-administration with strong CYP3A4 inducers is not recommended, except for selected anticonvulsants (LIVTENCITY Product Label). Co-administration of maribavir with rifabutin, a moderate CYP3A4 inducer, could potentially result in a > 50% decrease in maribavir exposure. Therefore, co-administration maribavir with rifabutin is not recommended due to potential for a decrease in efficacy of maribavir (LIVTENCITY Product Label). PBPK modeling and simulations were conducted to predict the effect of concomitant anticonvulsants on maribavir PK. Co-administration of carbamazepine and phenytoin, both strong CYP3A4 inducers, and phenobarbital, a moderate CYP3A4 inducer, was predicted to decrease maribavir AUC by 30%, 43%, and 40%, respectively. According to the Product Label, the dosage of maribavir should be increased to 800 mg twice daily if maribavir is co-administered with carbamazepine, and to 1200 mg twice daily if co-administered with phenytoin or phenobarbital. In addition, co-administration with efavirenz, a moderate CYP3A4 inducer, was predicted to decrease maribavir AUC up to 44%.

As a precipitant, maribavir is a weak inhibitor of CYP3A4. In vivo, co-administration of maribavir with tacrolimus, an immunosuppressant and also a CYP3A4 sensitive substrate, increased tacrolimus AUC 1.54-fold. According to the Product Label, co-administration of maribavir with drugs that are sensitive substrates of CYP3A4 may result in a clinically relevant increase in plasma concentrations of these substrates.

Maribavir showed weak inhibition of CYP2C19 in a cocktail study, with a 1.71-fold increase in plasma omeprazole/5-hydroxyomeprazole ratio observed. The effect on CYP2C19 is not considered to be clinically meaningful.

Maribavir is considered an inhibitor of P-gp and BCRP. In vivo, co-administration of maribavir with digoxin, a P-gp substrate, increased digoxin AUC and Cmax 1.22- and 1.26-fold, respectively. Based on the in vitro results, maribavir has the potential to inhibit BCRP in vivo. However, no in vivo studies were conducted to evaluate the clinical relevance of BCRP inhibition. According to the Product Label, co-administration of maribavir with drugs that are sensitive substrates of P-gp or BCRP may result in a clinically relevant increase in plasma concentrations of these substrates. It is recommended to use caution when maribavir and digoxin are co-administered and monitor serum digoxin concentrations. The dose of digoxin may need to be reduced when co-administered with maribavir (LIVTENCITY Product Label). When maribavir is co-administered with rosuvastatin, patients should be closely monitored for rosuvastatin-related events, especially the occurrences of myopathy and rhabdomyolysis (LIVTENCITY Product Label).

According to the Product Label, maribavir 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). It is recommended to adjust the immunosuppressant dose, as needed, and frequently monitor immunosuppressant levels throughout treatment with maribavir, especially following initiation and after discontinuation of maribavir (LIVTENCITY Product Label Warnings and Precautions).

Regarding organ impairment, no clinically significant differences in the PK of maribavir were observed in clinical studies in subjects with moderate hepatic impairment, mild-to-moderate renal impairment, or severe renal impairment. The effect of severe hepatic impairment or end stage renal disease, including dialysis, was not studied.

A moderate-fat meal did not significantly affect maribavir PK. Maribavir can be taken with or without food (LIVTENCITY Product Label).

Main routes of elimination

Extensive Metabolism

Following a single oral dose of 400 mg radiolabeled maribavir, 14% of the dose was excreted in feces (5.7% as unchanged maribavir) and 61% excreted in the urine (< 2% as unchanged maribavir). Maribavir was the predominant moiety in plasma (88%), followed by the inactive metabolite VP44469 (12%). The AUC ratio of VP44469 to maribavir in plasma was 14-35%.

Hepatic impairment: In a dedicated hepatic impairment study, following administration of 400 mg single dose of maribavir the AUC and Cmax of maribavir were 1.31- and 1.19-fold higher, respectively, in subjects with moderate hepatic impairment (Child-Pugh class B) compared to controls with normal hepatic function. These changes in maribavir exposure are not considered to be clinically relevant. No dosage adjustment for maribavir is recommended for patients with mild or moderate hepatic renal impairment (LIVTENCITY Product Label). The PK of maribavir in patients with severe hepatic impairment has not been studied.

Renal impairment: In a dedicated renal impairment study, a single 400 mg dose of maribavir was administered to subjects with mild-to-moderate (CLcr: 30-80 mL/min) or severe renal impairment (CLcr < 30 mL/min), and controls with normal renal function. The AUC and Cmax of maribavir were unchanged in subjects with renal impairment compared to controls. According to the Product Label, no dosage adjustment for maribavir is recommended for patients with mild, moderate, or severe renal impairment (LIVTENCITY Product Label). The PK of maribavir in patients with end stage renal disease, including patients on dialysis, has not been studied.

Food effect: In a food-effect study conducted in healthy volunteers, a moderate-fat meal decreased the AUC and Cmax of maribavir (400 mg single dose) by 14% and 28%, respectively, and delayed Tmax by 0.5 h, compared to fasted conditions. According to the Product Label, maribavir can be taken with or without food.

Main enzymes and associated interactions

CYP3A4

In vitro studies have shown that maribavir is biotransformed into the major metabolite VP44469 (N-dealkylated metabolite), with a metabolic ratio of 0.15-0.20. CYP3A4 was identified as the primary enzyme involved in the metabolism of maribavir, with minor contribution of CYP1A2 and multiple UGTs (UGT1A1, UGT1A3, UGT1A9, and UGT2B7).

In vivo, co-administration of maribavir (400 mg single dose) with ketoconazole (400 mg single dose), a strong CYP3A4 inhibitor (also a P-gp inhibitor), increased maribavir AUC and Cmax 1.54- and 1.10-fold, respectively. Population PK analysis demonstrated that strong CYP3A4 inhibitors (used in 22% transplant patients with CMV) had a significant impact on maribavir PK with a 30% lower clearance. PBPK modeling and simulations were also conducted to predict the effect of concomitant CYP3A4 inhibitors on the PK of maribavir (400 mg single dose). Co-administration of ketoconazole (400 mg once daily) and ritonavir (100 mg twice daily), both strong CYP3A4 inhibitors, was predicted to increase maribavir AUC 1.46- and 1.61-fold, respectively. Co-administration of diltiazem (60 mg three times daily) and erythromycin (500 mg three times daily), both moderate CYP3A4 inhibitors, was predicted to increase maribavir AUC 1.09- and 1.43-fold, respectively. However, these changes in maribavir exposure are not expected to be clinically significant due to its safety profile.

On the other hand, maribavir is sensitive to induction. Concomitant administration of maribavir (400 mg single dose) with rifampin (600 mg once daily for 12 days), a strong CYP3A4 inducer (and a P-gp inducer), decreased maribavir AUC, Cmax, and Cmin by 60%, 39%, and 82%, respectively. Population PK analysis demonstrated that strong CYP3A4 inducers (used in 1% transplant patients with CMV) had a significant impact on maribavir PK with a 2.24-fold higher clearance. According to the Product Label, co-administration with strong CYP3A4 inducers is not recommended, except for selected anticonvulsants. Based on the rifampin data, concomitant use of maribavir with rifabutin, a moderate CYP3A4 inducer, could potentially result in a > 50% decrease in maribavir exposure. Therefore, co-administration maribavir with rifabutin is not recommended due to potential for a decrease in efficacy of maribavir (LIVTENCITY Product Label). PBPK modeling and simulations were conducted to predict the effect of anticonvulsants and CYP3A4 inducers on the PK of maribavir (400 mg twice daily). Co-administration of carbamazepine (400 mg twice daily) and phenytoin (300 mg once daily), both anticonvulsants and strong CYP3A4 inducers, was predicted to decrease maribavir AUC up to 30% and 43%, respectively. Co-administration of phenobarbital (100 mg once daily), also an anticonvulsant and moderate CYP3A4 inducer, was predicted cause a decrease in maribavir AUC up to 40%. Further, when maribavir dose was increased to 800 mg or 1200 mg twice daily, co-administration with these drugs was predicted to increase maribavir AUC 1.40- to 1.80-fold, which is not considered to be clinically significant. Based on the simulated data, the dosage of maribavir should be increased to 800 mg twice daily if maribavir is co-administered with carbamazepine. If maribavir is co-administered with phenytoin or phenobarbital, the dosage of maribavir should be increased to 1200 mg twice daily (LIVTENCITY Product Label). In addition, co-administration with efavirenz (600 mg once daily), a moderate CYP3A4 inducer, was predicted to decrease maribavir (400 mg twice daily) AUC up to 44%.

Main transporters and associated interactions

In vitro studies suggest that maribavir is a substrate of P-gp, BCRP, and OCT1, but not of OATP1B1, OATP1B3, or BSEP. P-gp may contribute to the change of maribavir exposure in the interactions discussed above as these drugs are also inhibitors or inducers of P-gp.

Inhibition profile

Enzymes

CYP3A4 **CYP2C19**

In vitro, maribavir inhibited CYP1A2 (IC50 = 40 μM, R1 = 1.06), CYP2C9 (IC50 = 18 μM, R1 = 1.14), CYP2C19 (IC50 = 35 μM, R1 = 1.07), and CYP3A4 (time-dependent but not reversible inhibition; value not provided). Maribavir metabolite VP44469 also inhibited CYP3A4 (IC50 = 30 μM, R1 = 1.04). Based on the R1 values (1 + Cmax,u/Ki,u) > 1.02, maribavir has the potential to inhibit these CYPs in vivo. A cocktail study was conducted in healthy subjects who were co-administered maribavir (400 mg twice daily for 10 days) with a single dose of the following substrates: caffeine (CYP1A2; 2 mg/kg), (S)-warfarin (CYP2C9; 10 mg as racemic warfarin), omeprazole (CYP2C19; 40 mg), dextromethorphan (CYP2D6; 30 mg), and midazolam (CYP3A; 0.075 mg/kg). Results showed a 1.71-fold increase in plasma omeprazole/5-hydroxyomeprazole ratio, indicating inhibition of CYP2C19, but no significant changes in the PK of the other substrates. The effect on CYP2C19 is not considered to be clinically meaningful. In addition, co-administration of voriconazole (200-400 mg twice daily for 7 days), a CYP2C19 moderate sensitive substrate, with maribavir (400 mg twice daily for 7 days) did not significantly affect the PK of voriconazole. In another clinical study, co-administration of maribavir (400 mg twice daily for 8 days) did not significantly affect the exposure of dextromethorphan (30 mg single dose).

Maribavir is considered a weak inhibitor of CYP3A4 based on the study with tacrolimus, a CYP3A4 sensitive substrate (also a P-gp substrate). Co-administration of maribavir (400 mg twice daily) with tacrolimus (0.5-16 mg twice daily) increased tacrolimus AUC and Cmax 1.54- and 1.33-fold, respectively. According to the Product Label, co-administration of maribavir with drugs that are sensitive substrates of CYP3A4 may result in a clinically relevant increase in plasma concentrations of these substrates (LIVTENCITY Product Label). Maribavir has the potential to increase drug concentrations of immunosuppressant drugs that are CYP3A4 substrates and/or P-gp substrates (cyclosporine, everolimus, sirolimus, and tacrolimus) where minimal concentration changes may lead to serious adverse events (see section below for the information about P-gp; PMID# 25089341, PMID# 25089341). It is recommended to adjust the immunosuppressant dose, as needed, and frequently monitor immunosuppressant levels throughout treatment with maribavir, especially following initiation and after discontinuation of maribavir (LIVTENCITY Product Label Warnings and Precautions).

Maribavir also weakly inhibited UGT1A1/1A3/1A9/2B7 (IC50 >= 32.3 μM). Based on the in vitro results, maribavir is not expected to cause clinically significant interactions with substrates of these UGTs. Maribavir did not inhibit CYP2A6, CYP2B6, CYP2C8, CYP2D6, CYP2E1, UGT1A4, or UGT1A6 in vitro (test concentrations not provided).

Transporters

P-gp (ABCB1) **BCRP (ABCG2)**

In vitro, maribavir inhibited P-gp (IC50 = 33.8 μM, Igut/IC50 = 126). In vivo, co-administration of maribavir (400 mg twice daily for 8 days) with digoxin (0.5 mg single dose), a P-gp substrate, increased digoxin AUC and Cmax 1.22- and 1.26-fold, respectively. According to the Product Label, co-administration of maribavir with drugs that are sensitive substrates of P-gp may result in a clinically relevant increase in plasma concentrations of these substrates. It is recommended to use caution when maribavir and digoxin are co-administered and monitor serum digoxin concentrations. The dose of digoxin may need to be reduced when co-administered with maribavir (LIVTENCITY Product Label). Regarding immunosuppressant drugs, as mentioned above, maribavir has the potential to increase drug concentrations of immunosuppressant drugs that are CYP3A4 substrates and/or P-gp substrates (cyclosporine, everolimus, sirolimus, and tacrolimus) where minimal concentration changes may lead to serious adverse events. It is recommended to adjust the immunosuppressant dose, as needed, and frequently monitor immunosuppressant levels throughout treatment with maribavir, especially following initiation and after discontinuation of maribavir (LIVTENCITY Product Label Warnings and Precautions).

In vitro, marabavir inhibited BCRP (IC50 = 7.05 μM, Igut/IC50 = 603). No in vivo studies were conducted to evaluate the clinical relevance. According to the Product Label, maribavir is considered an inhibitor of BCRP. Co-administration of maribavir with drugs that are sensitive substrates of BCRP may result in a clinically relevant increase in plasma concentrations of these substrates. When maribavir is co-administered with rosuvastatin, a substrate of BCRP, patients should be closely monitored for rosuvastatin-related events, especially the occurrences of myopathy and rhabdomyolysis (LIVTENCITY Product Label).

Maribavir also inhibited OATP1B1 (IC50 = 45.5 μM), OATP1B3 (IC50 = 49.1 μM), OAT3 (IC50 = 33.3 μM), MATE1 (IC50 = 20.4 μM), OCT1 (IC50 = 344 μM), and BSEP (IC50 = 46.5 μM) in vitro. However, none of them is considered to be clinically relevant. In vitro, maribavir did not inhibit OCT2, OAT1, or MATE2-K.

Induction profile

Enzymes

In vitro, maribavir induced CYP3A4, but not CYP1A2 or CYP2B6 (details not provided).

Transporters

The induction potential of maribavir and its metabolite on drug transporters was not evaluated.

Other DDIs

Absorption-based DDI: Co-administration of maribavir (100 mg single dose) with antacid (20 mL single dose, containing aluminum hydroxide 800 mg and magnesium hydroxide 800 mg) did not significantly affect maribavir PK.

Other DDIs: The use of maribavir is not recommended with valganciclovir or ganciclovir, and may antagonize antiviral activity (LIVTENCITY Product Label).

Other PK studies: In a population PK analysis, no clinically significant differences in maribavir PK based on age (18-79 years), gender, race (Caucasian, Black, Asian, or others), ethnicity (Hispanic/Latino or non-Hispanic/Latino), or body weight (36-141 kg) were observed.

QT summary

Sources

Drugs@FDA - Clinical Reviews **Drugs@FDA - Product Labels** **PubMed 32506738**

Preclinical data

In vitro, maribavir had no effect on hERG tail current at 1254 μg/mL.

Clinical data

No QTc prolongation - Thorough QT (TQT) study

Measurement Means (CI)	**Test**	**Positive control** moxifloxacin
Dose Regimen	100 mg and 1200 mg single dose	400 mg single dose
Population	healthy volunteers	healthy volunteers
Mean change in QTc Fridericia (msec)	100 mg: 1.24 (-1.33, 3.80) at 3 h; 1200 mg: 2.37 (-0.19, 4.93) at 3 h	8.95 (6.40, 11.50) at 3 h
Slope linear regression	-0.0260 µg/mL*msec (P < 0.001)	

In a randomized, placebo- and positive-controlled, four-period crossover thorough QT study in healthy volunteers, maribavir (100 mg and 1200 mg) did not prolong the QT interval to any clinically relevant extent. The supratherapeutic dose of maribavir (1200 mg, three times higher than the recommended 400 mg dose) was investigated to represent the worst-case scenario of increased maribavir exposures due to concomitant use of a strong CYP3A inhibitor.

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