

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LIVTENCITY safely and effectively. See full prescribing information for LIVTENCITY

LIVTENCITY (maribavir) tablets, for oral use

Initial U.S. Approval: 2021

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. (1, 8.4)

DOSAGE AND ADMINISTRATION

400 mg (two 200 mg tablets) orally twice daily with or without food. (2.1, 2.2, 8.4)

DOSAGE FORMS AND STRENGTHS

Tablets: 200 mg of maribavir. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- LIVTENCITY may antagonize the antiviral activity of ganciclovir and valganciclovir. Coadministration is not recommended. (5.1, 7.1)
- 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. (5.2, 12.4, 14.1)

- 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. (5.1, 5.3, 7.1, 7.2, 7.3)
- 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. (5.3)

ADVERSE REACTIONS

The most common adverse events (all grades, >10%) in subjects treated with LIVTENCITY were taste disturbance, nausea, diarrhea, vomiting, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals America, Inc. at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Refer to the full prescribing information for important drug interactions with LIVTENCITY. (5.1, 5.3, 7)
- Coadministration with strong CYP3A4 inducers: not recommended. Refer to full prescribing information for dosage modification when coadministered with certain anticonvulsants. (2.2, 7.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2021

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LIVTENCITY is indicated for the treatment of adults and pediatric patients (12 years of age and older and weighing at least 35 kg) with post-transplant cytomegalovirus (CMV) infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir or foscarnet [see *Use in Specific Populations (8.4), Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

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 [see *Use in Specific Populations (8.4), Clinical Pharmacology (12.3), Clinical Studies (14)*].

2.2 Dosage Adjustment When Co-administered with Anticonvulsants

If LIVTENCITY is co-administered with carbamazepine, increase the dosage of LIVTENCITY to 800 mg twice daily [see *Drug Interactions (7.3)*].

If LIVTENCITY is co-administered with phenytoin or phenobarbital, increase the dosage of LIVTENCITY to 1,200 mg twice daily [see *Drug Interactions (7.3)*].

3 DOSAGE FORMS AND STRENGTHS

Tablet: 200 mg, blue, oval shaped convex tablet debossed with “SHP” on one side and “620” on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Reduced Antiviral Activity When Coadministered with Ganciclovir and Valganciclovir

LIVTENCITY may antagonize the antiviral activity of ganciclovir and valganciclovir by inhibiting human CMV pUL97 kinase, which is required for activation/phosphorylation of ganciclovir and valganciclovir. Coadministration of LIVTENCITY with ganciclovir or valganciclovir is not recommended [see *Drug Interactions (7.1) and Microbiology (12.4)*].

5.2 Virologic Failure During Treatment and Relapse Post-Treatment

Virologic failure due to resistance can occur during and after treatment with LIVTENCITY. Virologic relapse during the posttreatment period usually occurred within 4-8 weeks after treatment discontinuation. Some maribavir pUL97 resistance-associated substitutions confer cross-resistance to ganciclovir and valganciclovir. Monitor CMV DNA levels and check for maribavir resistance if the patient is not responding to treatment or relapses [see *Microbiology (12.4) and Clinical Studies (14.1)*].

5.3 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

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 (7)*].

See Table 3 for steps to prevent or manage these possible or known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during LIVTENCITY therapy; review concomitant medications during LIVTENCITY therapy and monitor for adverse reactions.

Maribavir is primarily metabolized by CYP3A4. Drugs that are strong inducers of CYP3A4 are expected to decrease maribavir plasma concentrations and may result in reduced virologic response; therefore, coadministration of LIVTENCITY with these drugs is not recommended, except for selected anticonvulsants [see Dosage and Administration (2.2) and Drug Interactions (7.3)].

Use with Immunosuppressant Drugs

LIVTENCITY has the potential to increase the drug concentrations of immunosuppressant drugs that are CYP3A4 and/or P-glycoprotein (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 immunosuppressant dose, as needed [see Drug Interactions (7.3) and Clinical Pharmacology (12.3)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of LIVTENCITY was evaluated in one Phase 3 multi-center, randomized, open-label, active-control trial in which 352 adult transplant recipients were randomized, and treated with LIVTENCITY (N=234) or Investigator-Assigned Treatment (IAT) consisting of monotherapy or dual therapy with ganciclovir, valganciclovir, foscarnet, or cidofovir as dosed by the investigator (N=116) for up to 8-weeks following a diagnosis of CMV infection/disease refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, foscarnet or cidofovir. The mean treatment durations (SD) for LIVTENCITY and IAT were 48.6 (\pm 13.82) and 31.2 (\pm 16.91) days, respectively. The most common adverse events occurring in more than 10% of subjects receiving LIVTENCITY are outlined in Table 1.

Table 1: Adverse Events (All Grades) Reported in >10% of Subjects in the LIVTENCITY Group in Trial 303

ADVERSE EVENT	LIVTENCITY N = 234 (%)	IAT ^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

Similar proportions of subjects experienced serious adverse events (38% in the LIVTENCITY group and 37% in the IAT group). The most common serious adverse event in both treatment groups occurred in the Infections and Infestations System Organ Class (SOC) (23% in the LIVTENCITY group and 15% in the IAT group) with CMV infection and disease being the most common in both groups.

A higher proportion of subjects in the IAT group discontinued study medication due to an adverse event compared to the LIVTENCITY group (32% in the IAT group versus 13% in the LIVTENCITY group). The most commonly reported causes that led to study drug discontinuation were neutropenia (9%) and acute kidney injury (5%) in the IAT group and dysgeusia, diarrhea, nausea, and recurrence of underlying disease (each reported at 1%) in the LIVTENCITY group.

Taste disturbance occurred in 46% of subjects treated with LIVTENCITY. These events rarely led to discontinuation of LIVTENCITY (1%) and, for 37% of the subjects, these events resolved while on therapy (median duration 43 days; range 7 to 59 days). For the subjects with ongoing taste disturbance after drug discontinuation, resolution occurred in 89%. In subjects with resolution of symptoms after drug discontinuation, the median duration of symptoms off treatment was 6 days (range 2 to 85 days).

Laboratory Abnormalities

Selected laboratory abnormalities reported in subjects with refractory (with or without genotypic resistance) CMV infections in Trial 303 are presented in Table 2.

Table 2: Selected Laboratory Abnormalities Reported in Trial 303

Laboratory Parameter	LIVTENCITY	IAT
	N=234 n (%)	N=116 n (%)
Neutrophils (cells / μ L)		
<500	4 (2)	4 (3)
\geq 500 to <750	7 (3)	7 (6)
\geq 750 to <1,000	10 (4)	6 (5)
Hemoglobin (g/dL)		
<6.5	3 (1)	1 (1)
\geq 6.5 to <8.0	34 (15)	23 (20)
\geq 8.0 to <9.5	76 (32)	33 (28)
Platelets (cells / μ L)		

<25,000	11 (5)	6 (5)
≥25,000 to <50,000	27 (12)	10 (9)
≥50,000 to <100,000	41 (18)	20 (17)
Creatinine (mg/dL)		
>2.5	16 (7)	12 (10)
>1.5 to ≤2.5	78 (33)	29 (25)

7 DRUG INTERACTIONS

7.1 Reduced Antiviral Activity When Coadministered with Ganciclovir or Valganciclovir

LIVTENCITY is not recommended to be coadministered with valganciclovir/ganciclovir (vGCV/GCV). LIVTENCITY may antagonize the antiviral activity of ganciclovir and valganciclovir by inhibiting human CMV pUL97 kinase, which is required for activation/phosphorylation of ganciclovir and valganciclovir [see *Warnings and Precautions (5.1) and Microbiology (12.4)*].

7.2 Potential for Other Drugs to Affect LIVTENCITY

Maribavir is a substrate of CYP3A4. Coadministration of LIVTENCITY with strong inducers of CYP3A4 is not recommended, except for selected anticonvulsants [see *Dosage and Administration (2.2) and Drug Interactions (7.3)*].

7.3 Potential for LIVTENCITY to Affect Other Drugs

Maribavir is a weak inhibitor of CYP3A4, and an inhibitor of P-gp and breast cancer resistance protein (BCRP). Co-administration of LIVTENCITY with drugs that are sensitive substrates of CYP3A, P-gp and BCRP may result in a clinically relevant increase in plasma concentrations of these substrates (see *Table 3*). *Table 3* provides a list of established or potentially clinically significant drug interactions, based on either clinical drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or decrease in efficacy [see *Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)*].

Table 3: Established and Other Potentially Significant Drug Interactions^a

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comments
Antiarrhythmics		
Digoxin ^b	↑ 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		
Rifabutin	↓ Maribavir	Co-administration of LIVTENCITY and rifabutin is not recommended due to potential for a decrease in efficacy of LIVTENCITY.
Rifampin ^b	↓ 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 ^c	↑ 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 ^b	↑ 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 [see *Clinical Pharmacology* (12.3)].

^c Refer to the respective prescribing information.

7.4 Drugs without Clinically Significant Interactions with LIVTENCITY

No clinically significant interactions were observed in clinical drug-drug interaction studies of LIVTENCITY and ketoconazole, antacid, caffeine, S-warfarin, voriconazole, dextromethorphan, or midazolam [see *Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

No adequate human data are available to establish whether LIVTENCITY poses a risk to pregnancy outcomes. In animal reproduction studies, embryo-fetal survival was decreased in rats, but not in rabbits, at maribavir exposures less than those observed in humans at the recommended human dose (RHD) (*see Data*).

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In a combined fertility and embryofetal development study, maribavir was administered to male and female rats at oral doses of 100, 200, or 400 mg/kg/day. Females were dosed for 15 consecutive days prior to pairing, throughout pairing, and up to gestation day (GD) 17, while males were dosed 29 days prior to mating and throughout mating. A decrease in the number of viable fetuses and increase in early resorptions and post-implantation losses were observed at ≥ 100 mg/kg/day (at exposures approximately half the human exposure at the RHD). Intermittent reduced body weight gain was observed in pregnant animals at ≥ 200 mg/kg/day. Maribavir had no effect on embryo-fetal growth or development at dose levels up to 400 mg/kg/day, at exposures similar to those observed in humans at the RHD.

No significant toxicological effects on embryo-fetal growth or development were observed in rabbits when maribavir was administered at oral doses up to 100 mg/kg/day from GD 8 to 20, at exposures approximately half the human exposure at the RHD.

In the pre- and postnatal developmental toxicity study maribavir was administered to pregnant rats at oral doses of 50, 150, or 400 mg/kg/day from GD 7 to postnatal day (PND) 21. A delay in developmental milestones was observed, including pinna detachment at doses ≥ 150 mg/kg/day and eye opening and preputial separation associated with reduced bodyweight gain of the offspring at 400 mg/kg/day. In addition, decreased fetal survival and litter loss was observed due to maternal toxicity and poor maternal care, respectively, at doses ≥ 150 mg/kg/day. No effects were observed at 50 mg/kg/day (which is estimated to be less than the human exposure at the RHD). No effects on number of offspring, proportion of males, number of live pups, or survival to PND 4 were observed at any dose in the offspring born to the second generation.

8.2 Lactation

Risk Summary

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. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LIVTENCITY and any potential adverse effects to the breast-fed child.

8.4 Pediatric Use

The recommended dosing regimen in pediatric patients 12 years of age and older and weighing at least 35 kg is the same as that in adults. Use of LIVTENCITY in this age group is based on the following:

- Evidence from controlled studies of LIVTENCITY in adults

- Population pharmacokinetic (PK) modeling and simulation demonstrating that age and body weight had no clinically meaningful effect on plasma exposures of LIVTENCITY
- LIVTENCITY exposure is expected to be similar between adults and children 12 years of age and older and weighing at least 35 kg
- The course of the disease is similar between adults and pediatric patients to allow extrapolation of data in adults to pediatric patients [see *Dosage and Administration (2.2)*, *Clinical Pharmacology (12.3)* and *Clinical Studies (14)*]

The safety and effectiveness of LIVTENCITY have not been established in children younger than 12 years of age.

8.5 Geriatric Use

No dosage adjustment is required for patients over 65 years of age based on the results from population pharmacokinetics analysis [see *Clinical Pharmacology (12.3)*] and efficacy and safety data from the clinical studies. In the clinical Study 303, 54 patients aged 65 years and over were treated with LIVTENCITY. Safety, effectiveness, and pharmacokinetics were consistent between elderly patients (≥ 65 years) and younger patients (< 65 years).

8.6 Impaired Renal Function

No dose adjustment of LIVTENCITY is needed for patients with mild, moderate, or severe renal impairment [see *Clinical Pharmacology (12.3)*]. Administration of LIVTENCITY in patients with end stage renal disease (ESRD), including patients on dialysis, has not been studied.

8.7 Impaired Hepatic Function

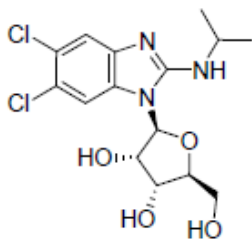
No dose adjustment of LIVTENCITY is needed for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment [see *Clinical Pharmacology (12.3)*]. Administration of LIVTENCITY in patients with severe hepatic impairment has not been studied.

10 OVERDOSAGE

There is no known specific antidote for LIVTENCITY. In case of overdose, it is recommended that the patient be monitored for adverse reactions and appropriate symptomatic treatment instituted. Due to the high plasma protein binding of LIVTENCITY, dialysis is unlikely to reduce plasma concentrations of LIVTENCITY significantly.

11 DESCRIPTION

LIVTENCITY tablets contain maribavir, a benzimidazole riboside CMV pUL97 protein kinase inhibitor. The chemical name of maribavir is 5,6-Dichloro-*N*-(1-methylethyl)-1- β -L-ribofuranosyl-1*H*-benzimidazol-2-amine and the structural formula is:



The molecular formula for maribavir is $C_{15}H_{19}Cl_2N_3O_4$ and its molecular weight is 376.23.

Each 200 mg tablet for oral administration contains 200 mg maribavir and the following inactive ingredients: FD&C Blue #1, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, sodium starch glycolate, titanium dioxide, and talc.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

LIVTENCITY is an antiviral drug against human CMV [*see Microbiology (12.4)*].

12.2 Pharmacodynamics

Exposure-response

In dose-ranging studies that evaluated doses of 400 mg twice daily and twice daily doses of two and three times the recommended dose, no exposure-response relationship was observed for viral load or probability of unquantifiable plasma CMV DNA.

In Phase 3 Trial 303 that evaluated a maribavir dose of 400 mg twice daily, increasing maribavir exposure was not associated with increased probability of confirmed plasma CMV DNA < LLOQ (lower limit of quantification) at Week 8.

Cardiac Electrophysiology

At three times the recommended dose (approximately twice the peak concentration observed following the recommended dose), LIVTENCITY does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

LIVTENCITY pharmacological activity is due to the parent drug. Following oral administration, plasma maribavir exposure (C_{\max} and AUC) increased approximately dose-proportionally following a single dose of 50 to 1600 mg (0.125 to four times the recommended dose) and multiple doses up to 2400 mg per day (three times the recommended daily dose). Maribavir PK is time-independent. With twice-daily dosing, steady state is reached within 2 days, with mean accumulation ratios of C_{\max} and AUC ranging from 1.37 to 1.47.

The pharmacokinetic properties of maribavir following administration of LIVTENCITY are displayed in Table 4. The multiple-dose pharmacokinetic parameters are provided in Table 5.

Table 4: Pharmacokinetic Properties of Maribavir

Absorption^a	
T _{max} (h), median	1.0 to 3.0
Distribution	
Mean apparent steady-state volume of distribution (V _{ss} , L)	27.3
% bound to human plasma proteins	98.0 across the concentration range of 0.05-200 µg/mL
Blood-to plasma ratio	1.37
Elimination	
Major route of elimination	Hepatic metabolism
Half-life (t _{1/2}) in transplant patients (h), mean	4.32
Oral clearance (CL/F) in transplant patients (L/h), mean	2.85
<i>Metabolism</i>	
Metabolic pathways ^b	CYP3A4 (major) and CYP1A2 (minor)
<i>Excretion</i>	
% of dose excreted as total ¹⁴ C (unchanged drug) in urine ^c	61 (<2)
% of dose excreted as total ¹⁴ C (unchanged drug) in feces ^c	14 (5.7)

^a When taken orally with a moderate fat meal versus fasted, the AUC_{0-∞} and C_{max} (geometric mean ratio [90% CI]) of maribavir are 0.864 [0.804, 0.929] and 0.722 [0.656, 0.793], respectively.

^b In vitro studies have shown that maribavir is biotransformed into a major circulating inactive metabolite: VP 44469 (N-dealkylated metabolite), with a metabolic ratio of 0.15 - 0.20

^c Dosing in mass balance study: single-dose administration of [¹⁴C] maribavir oral solution 400 mg containing 200 nCi of total radioactivity.

Table 5. Multiple-Dose Pharmacokinetic Parameters of Maribavir

Geometric Mean (%CV) ^a		
AUC _{0-tau} ^b (µg•h/mL)	C _{max} (µg/mL)	C _{tau} (µg/mL)
128 (50.7%)	17.2 (39.3%)	4.90 (89.7%)

CV = Coefficient of Variation; C_{max} = Maximum concentration; AUC_{0-tau} = Area under the time concentration curve over a dosing interval; C_{tau} = Concentration at the end of a dosing interval.

^a Pharmacokinetic parameter values based on post-hoc estimates from maribavir population pharmacokinetic model in transplant patients with CMV receiving 400 mg of LIVTENCITY twice daily with or without food.

^b tau is maribavir dosing interval: 12 hours

Specific Populations

There were no clinically significant differences in the pharmacokinetics of maribavir based on age (18-79 years), gender, race (Caucasian, Black, Asian, or others), ethnicity (Hispanic/Latino or non-Hispanic/Latino),

body weight (36 to 141 kg), mild to severe renal impairment (measured creatinine clearance ranging from 12 to 70 mL/min), or mild to moderate hepatic impairment (Child-Pugh Class A or B).

Pediatric Patients

The pharmacokinetics of maribavir in patients less than 18 years of age have not been evaluated.

Using modeling and simulation, the recommended dosing regimen is expected to result in comparable steady-state plasma exposures of maribavir in patients 12 years of age and older and weighing at least 35 kg as observed in adults [see *Use in Specific Populations (8.4)*].

Drug Interactions

Based on in vitro studies, the metabolism of maribavir is not mediated by CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A5, UGT1A4, UGT1A6, UGT1A10, or UGT2B15. The transport of maribavir is not mediated by organic anion transporting polypeptide (OATP)1B1, OATP1B3, or bile salt export pump (BSEP).

At clinically relevant concentrations, clinically significant interactions are not expected when LIVTENCITY is co-administered with substrates of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, CYP2D6, CYP3A4; uridine diphosphate-glucuronosyltransferase (UGT)1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7; P-gp; BSEP; multidrug and toxin extrusion protein (MATE)1/2K; organic anion transporters (OAT)1 and OAT3; organic cation transporters (OCT)1 and OCT2; OATP1B1 and OATP1B3. In a clinical drug-drug interaction cocktail study, coadministration with maribavir had no effect on substrates of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.

Drug interaction studies were performed with LIVTENCITY and other drugs likely to be co-administered for pharmacokinetic interactions. The effects of co-administration of other drugs on the pharmacokinetics of maribavir are summarized in Table 6, and the effects of maribavir on the pharmacokinetics of co-administered drugs are summarized in Table 7.

Dosing recommendations as a result of established and other potentially significant drug-drug interactions with LIVTENCITY are provided in Table 3 [see *Drug Interactions (7.3)*].

Table 6: Changes in Pharmacokinetics of LIVTENCITY in the Presence of Co-administered Drugs

Co-administered Drug and Regimen		LIVTENCITY Regimen	N	Geometric Mean Ratio (90% CI) of LIVTENCITY PK with/without Co-administered Drug [No Effect=1.00]		
				AUC	C _{max}	C _{tau} ^c
Anticonvulsants						
Carbamazepine ^a	400 mg once daily	800 mg twice daily / 400 mg twice daily	200	1.40 (1.09, 1.67)	1.53 (1.22, 1.79)	1.05 (0.71, 1.40)
Phenobarbital ^a	100 mg once daily	1,200 mg twice daily / 400 mg twice daily	200	1.80 (1.18, 2.35)	2.17 (1.69, 2.57)	0.94 (0.22, 1.97)
Phenytoin ^a	300 mg once daily	1,200 mg twice daily / 400 mg twice daily	200	1.70 (1.06, 2.46)	2.05 (1.49, 2.63)	0.89 (0.26, 2.04)
Antimycobacterials						
Rifampin	600 mg once daily	400 mg twice daily	14	0.40 (0.36, 0.44)	0.61 (0.52, 0.72)	0.18 (0.14, 0.25)
Antifungals						

Ketoconazole	400 mg single dose	400 mg single dose	19	1.53 (1.44, 1.63)	1.10 (1.01, 1.19)	-
Antacids						
Aluminum hydroxide and magnesium hydroxide antacid	20 mL ^b single dose	100 mg single dose	15	0.89 (0.83, 0.96)	0.84 (0.75, 0.94)	-

^a Based on physiologically based pharmacokinetic modeling results from 10 trials of 20 subjects each. The maribavir dosing regimen and geometric mean ratios (5th percentile, 95th percentile) correspond to dose-adjusted maribavir with inducer vs 400 mg twice daily without inducer.

^b Containing 800 mg aluminum hydroxide and 800 mg magnesium hydroxide.

^c tau is maribavir dosing interval: 12 hours

Table 7: Drug Interactions: Changes in Pharmacokinetics for Co-administered Drug in the Presence of 400 mg Twice Daily LIVTENCITY

Co-administered Drug and Regimen		N	Geometric Mean Ratio (90% CI) of Co-administered Drug PK with/without LIVTENCITY [No Effect=1.00]		
			AUC	C _{max}	C _{tau}
Immunosuppressants					
Tacrolimus	stable dose, twice daily (total daily dose: 0.5-16 mg)	20	1.51 (1.39, 1.65)	1.38 (1.20, 1.57)	1.57 (1.41, 1.74)
P-gp substrate					
Digoxin	0.5 mg single dose	18	1.21 (1.10, 1.32)	1.25 (1.13, 1.38)	-

12.4 Microbiology

Mechanism of Action

The antiviral activity of maribavir 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 IC₅₀ value of 0.003 μM. Maribavir and its 5'-mono- and 5'-triphosphate derivatives at 100 μM had no significant effect on the incorporation of deoxynucleoside triphosphates by human CMV DNA polymerase. At a concentration of 100 μM, 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%.

Antiviral Activity

Maribavir inhibited human CMV replication in virus yield reduction, DNA hybridization, and plaque reduction assays in human lung fibroblast cell line (MRC-5), human embryonic kidney (HEK), and human foreskin fibroblast (MRHF) cells. The EC₅₀ values ranged from 0.03 to 2.2 μM depending on the cell line and assay endpoint. The cell culture antiviral activity of maribavir has also been evaluated against CMV clinical isolates. The median EC₅₀ values were 0.1 μM (n=10, range 0.03-0.13 μM) and 0.28 μM (n=10, range 0.12-0.56 μM) using DNA hybridization and plaque reduction assays, respectively. No significant difference in EC₅₀ values across the four human CMV glycoprotein B genotypes (N = 2, 1, 4, and 1 for gB1, gB2, gB3, and gB4, respectively) was seen.

Combination Antiviral Activity

When maribavir was tested in combination with other antiviral compounds, antagonism of the antiviral activity was seen in combination with ganciclovir. No antagonism was observed with cidofovir, foscarnet, letermovir and rapamycin at the drugs EC₅₀ values. The pUL97 kinase activity inhibited by maribavir is necessary to activate valganciclovir/ganciclovir.

Viral Resistance

In Cell Culture

Selection of maribavir resistant virus in cell culture and genotypic plus phenotypic characterization of these has identified amino acid substitutions that confer reduced susceptibility to maribavir. Substitutions identified in pUL97 include L337M, V353A, L397R, T409M, and H411L/N/Y. These substitutions confer reductions in susceptibility that range from 3.5-fold to >200-fold. Substitutions were also identified in pUL27:R233S, W362R, W153R, L193F, A269T, V353E, L426F, E22stop, W362stop, 218delC, and 301-311del. These substitutions confer reductions in susceptibility that range from 1.7- to 4.8-fold.

In Clinical Studies

In Phase 2 Study 202 evaluating maribavir in 120 hematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT) recipients with phenotypic resistance to valganciclovir/ganciclovir, DNA sequence analysis of a select region of pUL97 (amino acids 270 to 482) and pUL27 (amino acids 108 to 424) was performed on 34 paired virologic failure samples. There were 25 patients with treatment-emergent maribavir resistance-associated substitution(s) in pUL97 F342Y (4.5-fold reduction in susceptibility), T409M (78-fold reduction), H411L/Y (69- and 12-fold reduction) and/or C480F (224-fold reduction).

In Phase 3 Study 303 evaluating maribavir in patients with phenotypic resistance to valganciclovir/ganciclovir, DNA sequence analysis of the entire coding regions of pUL97 and pUL27 was performed on 134 paired sequences from maribavir-treated patients. The treatment-emergent pUL97 substitutions F342Y (4.5-fold), T409M (78-fold), H411L/N/Y (69-, 9-, and 12-fold, respectively), and/or C480F (224-fold) were detected in 58 subjects (47 subjects were on-treatment failures and 11 subjects were relapsers). One subject with the pUL27 L193F substitution (2.6-fold reduced susceptibility to maribavir) at baseline did not meet the primary endpoint.

Cross Resistance

Cross-resistance has been observed between maribavir and ganciclovir/valganciclovir in cell culture and in clinical studies.

pUL97 valganciclovir/ganciclovir resistance-associated substitutions F342S/Y, K355del, V356G, D456N, V466G, C480R, P521L, and Y617del reduce susceptibility to maribavir >4.5-fold. Other vGCV/GCV resistance pathways have not been evaluated for cross-resistance to maribavir. pUL54 DNA polymerase substitutions conferring resistance to vGCV/GCV, cidofovir, or foscarnet remained susceptible to maribavir.

Substitutions pUL97 F342Y and C480F are maribavir treatment-emergent resistance-associated substitutions that confer >1.5-fold reduced susceptibility to vGCV/GCV, a fold reduction that is associated with phenotypic resistance to vGCV/GCV. The clinical significance of this cross-resistance to vGCV/GCV for these substitutions has not been determined. Maribavir resistant virus remained susceptible to cidofovir and foscarnet. Additionally, there are no reports of any pUL27 maribavir resistance-associated substitutions being evaluated for vGCV/GCV, cidofovir, or foscarnet cross-resistance. Given the lack of resistance-associated substitutions for these drugs mapping to pUL27, cross-resistance is not expected for pUL27 maribavir substitutions.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted in mice and rats administered oral doses up to 150 and 100 mg/kg/day, respectively. Maribavir was not carcinogenic in rats at any dose tested, corresponding to maribavir exposures less than human exposure at the RHD. At 150 mg/kg/day in male mice only, an increased incidence of hemangioma, hemangiosarcoma, and combined hemangioma/hemangiosarcoma was observed across multiple tissues, at exposures less than the human exposure at the RHD. There were no carcinogenic findings in male mice at ≤ 75 mg/kg/day and female mice at any dose.

Mutagenicity

Maribavir was negative in a bacterial mutation assay and the *in vivo* rat bone marrow micronucleus assay. Maribavir was positive in the absence of metabolic activation in the mouse lymphoma assay, and the results were equivocal in the presence of metabolic activation.

Impairment of Fertility

Although decreased sperm straight line velocity was observed in males (at maribavir exposures less than those observed in humans at the RHD), there were no effects on fertility in males or females in a combined oral fertility and embryo-fetal study in rats administered maribavir at up to 400 mg/kg/day [see *Use in Specific Populations (8.1)*].

14 CLINICAL STUDIES

14.1 Treatment of Adults with Post-transplant CMV Infection/Disease That Is Refractory (with or without Genotypic Resistance) to Ganciclovir, Valganciclovir, Cidofovir, or Foscarnet

LIVTENCITY was evaluated in a Phase 3, multicenter, randomized, open-label, active-controlled superiority trial (NCT02931539, Trial 303) to assess the efficacy and safety of LIVTENCITY compared to Investigator-Assigned Treatment (IAT) (ganciclovir, valganciclovir, foscarnet, or cidofovir) in 352 HSCT or SOT recipients with CMV infections that were refractory to treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir, including CMV infections with or without confirmed resistance to 1 or more of the IATs. Subjects with CMV disease involving the central nervous system, including the retina, were excluded from the study.

Subjects were stratified by transplant type (HSCT or SOT) and screening CMV DNA levels and then randomized in a 2:1 allocation ratio to receive either LIVTENCITY 400 mg twice daily or IAT as dosed by the investigator for up to 8 weeks. After completion of the treatment period, subjects entered a 12-week follow-up phase.

The mean age of trial subjects was 53 years and most subjects were male (61%), white (76%) and not Hispanic or Latino (83%), with similar distributions across the two treatment arms. The most common treatment used in the IAT arm was foscarnet which was administered in 47 (41%) subjects followed by ganciclovir or valganciclovir, each administered in 28 (24%) subjects. Cidofovir was administered in 6 subjects, the combination of foscarnet and valganciclovir in 4 subjects and the combination of foscarnet and ganciclovir in 3 subjects. Baseline disease characteristics are summarized in Table 8 below.

Table 8: Summary of Baseline Disease Characteristics in Trial 303

Characteristic	LIVTENCITY 400 mg Twice Daily N=235 n (%)	IAT N=117 n (%)
Transplant type		
HSCT	93 (40)	48 (41)
SOT	142 (60)	69 (59)
Kidney	74 (52)	32 (46)
Lung	40 (28)	22 (32)
Heart	14 (10)	9 (13)
Other (multiple, liver, pancreas, intestine)	14 (10)	6 (9)
CMV DNA levels		
Low (<9,100 IU/mL)	153 (65)	85 (73)
Intermediate (≥9,100 to <91,000 IU/mL)	68 (29)	25 (21)
High (≥91,000 IU/mL)	14 (6)	7 (6)
Confirmed symptomatic CMV infection at baseline		
No	214 (91)	109 (93)
Yes ^a	21 (9)	8 (7)
CMV syndrome (SOT only)	9 (43)	7 (88)
Tissue Invasive disease	12 (57) ^a	1 (13)

CMV=cytomegalovirus, DNA=deoxyribonucleic acid, HSCT=hematopoietic stem cell transplant, IAT=investigator assigned anti-CMV treatment, N=number of patients, SOT=solid organ transplant

^a one of the subjects had both CMV syndrome and disease but was counted for CMV disease only

Primary Efficacy Endpoint

The primary efficacy endpoint was 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. The key secondary endpoint was CMV DNA level < LLOQ and CMV infection symptom control at the end of Study Week 8 with maintenance of this treatment effect through Study Week 16.

For the primary endpoint, LIVTENCITY was statistically superior to IAT (56% vs. 24%, respectively), as shown in Table 9.

Table 9: Primary Efficacy Endpoint Analysis at Week 8 (Randomized Set) in Trial 303

	LIVTENCITY 400 mg Twice Daily N=235 n (%)	IAT N=117 n (%)
Primary Endpoint: Confirmed CMV DNA Level < LLOQ at Week 8^a		
Responders	131 (56)	28 (24)
Adjusted difference in proportion of responders (95% CI) ^b	33 (23, 43)	
p-value: adjusted ^b	<0.001	

CI=confidence interval; CMV=cytomegalovirus; IAT=investigator-assigned anti-CMV treatment; N=number of patients.

^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 [ie, <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 reasons for failure to meet the primary endpoint are summarized in Table 10.

Table 10: Analysis of Failures for Primary Efficacy Endpoint

Outcome at Week 8	LIVTENCITY N=235 n (%)	IAT N=117 n (%)
Responders (Confirmed DNA Level < LLOQ)^a	131 (56)	28 (24)
Non-responders:	104 (44)	89 (76)
Due to virologic failure^b:	80 (34)	42 (36)
• CMV DNA never < LLOQ	48 (20)	35 (30)
• CMV DNA breakthrough ^b	32 (14)	7 (6)
Due to drug/study discontinuation:	21 (9)	44 (38)
• Adverse events	8 (3)	26 (22)
• Deaths	10 (4)	3 (3)
• Withdrawal of consent	1 (<1)	9 (8)
• Other reasons ^c	2 (1)	6 (5)
Due to other reasons but remained on study^d	3 (1)	3 (3)

CMV=Cytomegalovirus, IAT=Investigator-assigned anti-CMV Treatment, MBV=maribavir.

Percentages are based on the number of subjects in the Randomized Set.

^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 [ie, <137 IU/mL]).

^b CMV DNA breakthrough=achieved confirmed CMV DNA level < LLOQ and subsequently became detectable.

^c Other reasons= other reasons not including adverse events, deaths and lack of efficacy, withdrawal of consent, and non-compliance.

^d Includes subjects who completed study assigned treatment and were non-responders.

The treatment effect of LIVTENCITY was consistent across transplant type, age group, and the presence of CMV syndrome/disease at baseline. However, LIVTENCITY was less effective against subjects with increased CMV DNA levels ($\geq 50,000$ IU/mL) and subjects with absence of genotypic resistance (*see Table 11*).

Table 11: Responders by Subgroup in Trial 303

	LIVTENCITY 400 mg Twice Daily N=235		IAT N=117	
	n/N	%	n/N	%
Transplant type				
SOT	79/142	56	18/69	26
HSCT	52/93	56	10/48	21
Baseline CMV DNA viral load				
Low (<9,100 IU/mL)	95/153	62	21/85	25
Intermediate ($\geq 9,100$ to <91,000 IU/mL)	32/68	47	5/25	20
$\geq 9,100$ to <50,000 IU/mL	29/59	49	4/20	20
$\geq 50,000$ to <91,000 IU/mL	3/9	33	1/5	20
High ($\geq 91,000$ IU/mL)	4/14	29	2/7	29
Genotypic resistance to other anti-CMV agents				
Yes	76/121	63	14/69	20
No	42/96	44	11/34	32
CMV syndrome/disease at baseline				
Yes	10/21	48	1/8	13
No	121/214	57	27/109	25
Age Group				
18 to 44 years	28/55	51	8/32	25
45 to 64 years	71/126	56	19/69	28
≥ 65 years	32/54	59	1/16	6

Secondary Endpoints

Table 12 shows results of the secondary endpoint, achievement of CMV DNA level < LLOQ and symptom control^a at Week 8 with maintenance through Week 16.

Table 12. Achievement of CMV DNA Level < LLOQ and CMV Infection Symptom Control at Week 8, With Maintenance Through Week 16^a

	LIVTENCITY 400 mg Twice Daily N=235 n (%)	IAT N=117 n (%)
Responders	44 (19)	12 (10)
Adjusted difference in proportion of responders (95% CI) ^b	9 (2,17)	
p-value: adjusted ^b	0.013	

^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.

Virologic relapse during follow-up period: After the end of treatment phase, 65/131 (50%) of subjects in the LIVTENCITY group and 11/28 (39%) subjects in the IAT group who achieved CMV DNA level < LLOQ experienced virologic relapse during the follow-up period. Most of the relapses 58/65 (89%) in LIVTENCITY group and 11/11 (100% in IAT group)] occurred within 4 weeks after study drug discontinuation; and the median time to relapse after CMV DNA level < LLOQ was 15 days (range 7, 71) in the LIVTENCITY group and 15 days (range 7, 29) in the IAT group [see *Warnings and Precautions (5.2) and Microbiology (12.4)*].

New onset symptomatic CMV infection: For the entire study period, a similar percentage of subjects in each treatment group developed new onset symptomatic CMV infection (LIVTENCITY 6% [14/235]; IAT 6% [7/113]).

Overall mortality: All-cause mortality was assessed for the entire study period. A similar percentage of subjects in each treatment group died during the trial (LIVTENCITY 11% [27/235]; IAT 11% [13/117]).

16 HOW SUPPLIED/STORAGE AND HANDLING

Tablet: 200 mg, blue, oval shaped convex tablet debossed with “SHP” on one side and “620” on the other side. They are supplied as follows:

Bottles of 28 tablets with child-resistant caps (NDC 64764-800-28)

Bottles of 56 tablets with child-resistant caps (NDC 64764-800-56)

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F), brief exposure to 15°C to 30°C (59°F to 86°F) permitted [see *USP Controlled Room Temperature*].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Inform patients that LIVTENCITY may interact with other drugs. Advise patients to report to their healthcare provider the use of any other medication [*see Warnings and Precautions (5.1 and 5.3), Drug Interactions (7)*].

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Takeda Pharmaceuticals America, Inc.

Lexington, MA 02421

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MAR358

Patient Information
LIVTENCITY (liv-TEN-city)
(maribavir)
tablets

What is LIVTENCITY?

LIVTENCITY is a prescription medicine used to treat cytomegalovirus (CMV) infection and disease in adults and children 12 years of age and older weighing at least 77 pounds (35 kg) who have received a transplant, when their infection or disease does not respond to treatment with the medicines ganciclovir, valganciclovir, cidofovir or foscarnet.

It is not known if LIVTENCITY is safe and effective in children under 12 years of age.

Before taking LIVTENCITY, tell your healthcare provider about all your medical conditions, including if you:

- are pregnant or plan to become pregnant. It is not known if LIVTENCITY will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if LIVTENCITY passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with LIVTENCITY.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. LIVTENCITY may affect the way other medicines work, and other medicines may affect how LIVTENCITY works and cause serious side effects.

Especially tell your healthcare provider if you take a seizure (anticonvulsant) medicine.

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with LIVTENCITY.
- **Do not start a new medicine without telling your healthcare provider.** Your healthcare provider will tell you if it is safe to take LIVTENCITY with other medicines.
- Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take LIVTENCITY?

- Take LIVTENCITY exactly as your healthcare provider tells you to take it.
- Take LIVTENCITY 2 times a day.
- Take LIVTENCITY with or without food.
- If you take too much LIVTENCITY, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of LIVTENCITY?

The most common side effects of LIVTENCITY include:

- | | |
|--------------------|-------------|
| • changes in taste | • vomiting |
| • nausea | • tiredness |
| • diarrhea | |

These are not all the possible side effects of LIVTENCITY.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store LIVTENCITY?

- Store LIVTENCITY at room temperature between 68°F to 77°F (20°C to 25°C).

Keep LIVTENCITY and all medicines out of the reach of children.

General information about the safe and effective use of LIVTENCITY.

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information leaflet. Do not use LIVTENCITY for a condition for which it was not prescribed. Do not give LIVTENCITY to other people, even

if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about LIVTENCITY that is written for health professionals.

What are the ingredients in LIVTENCITY?

Active ingredient: maribavir

Inactive ingredients: FD&C Blue #1, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, sodium starch glycolate, titanium dioxide, and talc.

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For more information, go to www.LIVTENCITY.com or call 1-877-TAKEDA-7 (1-877-825-3327)

This Patient Information has been approved by the U.S. Food and Drug Administration.

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