1 NAME OF THE MEDICINAL PRODUCT

LIVTENCITY®

1.1 DOSAGE FORMS AND STRENGTHS

Each film coated Tablet contains 200 mg maribavir. The film coated tablet is blue, oval shaped convex tablet debossed with “SHP” on one side and “620” on the other side.

2 THERAPUTIC INDICATION

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) and Clinical Studies (14)]*.

3 DOSAGE AND ADMINISTRATION

3.1 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) and Clinical Studies (14)]*.

3.2 Dosage Adjustment When Coadministered with Anticonvulsants

If LIVTENCITY is coadministered with carbamazepine, increase the dosage of LIVTENCITY to 800 mg (four 200 mg tablets) twice daily *[see Drug Interactions (7.3)]*.

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

3.3 Administration

The immediate-release tablets can be taken as whole, dispersed or crushed tablets by mouth, or as dispersed tablets through a nasogastric or orogastric tube (French size 10 or larger). The suspension may be prepared ahead of time and stored under 25°C for up to 8 hours.

Administration of Dispersed Tablets or Crushed Tablets by Mouth

1. Place the appropriate number of tablets for the prescribed dose into a suitable container. If desired, the tablets may be crushed. Add the appropriate volume of drinking water (other liquids have not been tested) to make a suspension *(see Table 1 below)*.

Table 1: Number of Tablets and Volume of Drinking Water Needed to Make a Suspension for Administration of Dispersed or Crushed Tablets by Mouth

Recommended Dosage	Number of 200 mg Tablets	Volume of Drinking Water
400 mg	Two	30 mL
800 mg	Four	60 mL
1,200 mg	Six	90 mL

2. Swirl the container gently to keep the particles from settling, and administer the suspension before it settles. The mixture will have a bitter taste.
3. Rinse the container with 15 mL of drinking water and administer the rinse water.
4. Repeat Step 3. Visually confirm that no particles are left in the container. If particles remain, repeat Step 3.

Administration of Dispersed Tablets through a Nasogastric (NG) or Orogastric (OG) Tube

1. Remove the cap (if applicable) and plunger out of a 50 or 60 mL catheter-tip compatible syringe or equivalent. Add two tablets into the syringe body and place the plunger back in the syringe. Only two tablets can be administered via NG or OG tube at a time.
2. Draw 30 mL of drinking water (other liquids have not been tested) into the syringe and hold the syringe with the tip pointing upward. Pull the plunger further to a higher volume position to have some air space in the syringe. Place the cap back on the syringe (if applicable). Shake the syringe well (careful not to spill the contents) for about 30 to 45 seconds or until the tablets are completely dispersed.
3. Once the tablets are completely dispersed in the syringe, remove the cap from the syringe again (if applicable) and attach the syringe to the NG or OG tube and administer the dispersion before it settles.
4. Draw 15 mL of water using the same syringe and flush through the same NG or OG tube.
5. Repeat Step 4 and make sure no particles are left in the syringe by visual inspection. If particles remain, repeat Step 4.
6. For doses of 800 mg (four 200 mg tablets) and 1,200 mg (six 200 mg tablets) *[see Dosage and Administration (3.2)]*, repeat Steps 1-5 until prescribed dose is reached. The same syringe, NG or OG tube can be used.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 11

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 post-treatment 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 4 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 (3.2) 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 multicenter, 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 (± 13.82) and 31.2 (± 16.91) days, respectively. The most common adverse events occurring in more than 10% of subjects receiving LIVTENCITY are outlined in Table 2.

Table 2: 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 vs 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 3.

Table 3: Selected Laboratory Abnormalities Reported in Trial 303

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

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 (3.2) 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). Coadministration 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 4)*. Table 4 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 4: 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 coadministered with carbamazepine.
Phenobarbital	↓ Maribavir	A dose adjustment of LIVTENCITY to 1,200 mg twice daily is recommended when coadministration with phenobarbital.
Phenytoin	↓ Maribavir	A dose adjustment of LIVTENCITY to 1,200 mg twice daily is recommended when coadministration with phenytoin.
Antimycobacterials		
Rifabutin	↓ Maribavir	Coadministration of LIVTENCITY and rifabutin is not recommended due to potential for a decrease in efficacy of LIVTENCITY.
Rifampin[b]	↓ Maribavir	Coadministration of LIVTENCITY and rifampin is not recommended due to potential for a decrease in efficacy of LIVTENCITY.
Herbal Products		
St. John's wort	↓ Maribavir	Coadministration 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 post-natal developmental toxicity study, maribavir was administered to pregnant rats at oral doses of 50, 150, or 400 mg/kg/day from GD 7 to post-natal 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 (3.2), 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

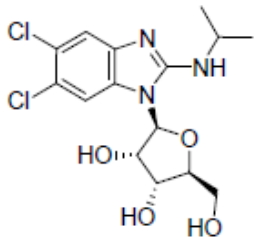
No dose adjustment of LIVTENCITY is needed for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment *[see Clinical Pharmacology (12.3)]*. Administration of LIVTENCITY in patients with severe hepatic impairment has not been studied.

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: core tablet: microcrystalline cellulose, sodium starch glycolate, magnesium stearate.

Opadry II Blue 85F105081 film coat: polyvinyl alcohol, macrogol/polyethylene glycol, titanium dioxide, talc and FD&C Blue #1.

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 5. The multiple-dose pharmacokinetic parameters are provided in Table 6.

Table 5: 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
Metabolism	
Metabolic pathways[b]	CYP3A4 (major) and CYP1A2 (minor)

Excretion	
% 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 vs fasted, the AUC0-∞ and Cmax (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 [^{14}C] maribavir oral solution 400 mg containing 200 nCi of total radioactivity.

Table 6: Multiple-Dose Pharmacokinetic Parameters of Maribavir

Geometric Mean (% CV)[a]		
$AUC_{0\text{-}tau}$[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; Cmax=Maximum concentration; $AUC_{0\text{-}tau}$=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 coadministered 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 coadministered for pharmacokinetic interactions. The effects of coadministration of other drugs on the pharmacokinetics of maribavir are summarized in Table 7, and the effects of maribavir on the pharmacokinetics of coadministered drugs are summarized in Table 8.

Dosing recommendations as a result of established and other potentially significant drug-drug interactions with LIVTENCITY are provided in Table 4 *[see Drug Interactions (7.3)]*.

Table 7: Changes in Pharmacokinetics of LIVTENCITY in the Presence of Coadministered Drugs

Coadministered Drug and Regimen		LIVTENCITY Regimen	N	Geometric Mean Ratio (90% CI) of LIVTENCITY PK with/without Coadministered 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 (5^{th} percentile, 95^{th} 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 8: Drug Interactions: Changes in Pharmacokinetics for Coadministered Drug in the Presence of 400 mg Twice Daily LIVTENCITY

Coadministered Drug and Regimen		N	Geometric Mean Ratio (90% CI) of Coadministered 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 IC_{50} 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 EC_{50} 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 EC_{50} 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 EC_{50} 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 EC_{50} values. The pUL97 kinase activity inhibited by maribavir is necessary to activate valganciclovir/ganciclovir.

Treatment Effect in CMV Glycoprotein B (gB) Subtypes

In Trial 303, the primary endpoint response rates for LIVTENCITY across CMV gB subtypes 1, 2, 3, 4, and 5 were 65% (55/85), 39% (22/57), 54% (22/41), 67% (14/21), and 64% (7/11), respectively. The primary endpoint response rates for IAT across CMV gB subtypes 1, 2, 3, 4, and 5 were 28% (15/53), 27% (4/15), 11% (2/19), 20% (2/10), and 17% (1/6), respectively *[see Clinical Studies (14)]*.

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 9 below.

Table 9: 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 10.

Table 10: 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 [i.e.;, <137 IU/mL]).
[b] Cochran-Mantel-Haenszel weighted average approach was used for the adjusted difference in proportion (maribavir – IAT), the corresponding 95% CI, and the p-value after adjusting for the transplant type and baseline plasma CMV DNA concentration. Only those with both stratification factors were included in the computation.

The reasons for failure to meet the primary endpoint are summarized in Table 11.

Table 11: 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 [i.e.;, <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 (≥50,000 IU/mL) and subjects with absence of genotypic resistance *(see Table 12)*.

Table 12: 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 (≥9,100 to <91,000 IU/mL)	32/68	47	5/25	20
≥9,100 to <50,000 IU/mL	29/59	49	4/20	20
≥50,000 to <91,000 IU/mL	3/9	33	1/5	20
High (≥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 13 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 13: 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]).

HOW SUPPLIED/STORAGE AND HANDLING

Bottles of 28 tablets with child-resistant caps

Bottles of 56 tablets with child-resistant caps

Not all packages may be marketed.

Storage and Handling

Do not store above 30°C.

The expiry date of the product is indicated on the packaging materials

17 MARKETING AUTHORISATION HOLDER

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18 MANUFACTURER

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19 MARKETING AUTHORISATION NUMBER(S)

173-33-37360-90

This PI was approved on August 2023, and is based on USPI approved on 26.04.23