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Swiss Public Assessment Report

LIVTENCITY

International non-proprietary name: maribavir
Pharmaceutical form: film-coated tablets
Dosage strength(s): 200 mg
Route(s) of administration: oral
Marketing authorisation holder: Takeda Pharma AG
Marketing authorisation no.: 68492
Decision and decision date: approved on 19 July 2023

Note:

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BID	*bis in die*, twice a day
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CMV	Cytomegalovirus
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMR	Geometric mean ratio
HIV	Human immunodeficiency virus
HPLC	High-performance liquid chromatography
IAT	Investigator-assigned anti-CMV treatment
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
MAR	Maribavir
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
QD	*quaque die;* once a day
RMP	Risk management plan
SAE	Serious adverse event
SCT	Stem cell transplant
SOC	System organ class
SOT	Solid organ transplant
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TID	*ter in die*; three times a day.

TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for maribavir in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA.
Orphan drug status was granted on 29 July 2021.

2.2 Indication and dosage

2.2.1 Requested indication

LIVTENCITY is indicated for the treatment of cytomegalovirus (CMV) infection and/or disease that are refractory (with or without resistance) to one or more prior therapies, including ganciclovir, valganciclovir, cidofovir, or foscarnet in adult patients who have undergone a haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT) (see section *Properties/Effects*).

2.2.2 Approved indication

LIVTENCITY is indicated for the treatment of cytomegalovirus (CMV) infection and/or disease that are refractory (with or without resistance) to one or more prior therapies, including ganciclovir, valganciclovir, cidofovir, or foscarnet in adult patients who have undergone a haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT) (see section *Properties/Effects*).

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dose of LIVTENCITY is 400 mg (2 × 200 mg tablets) twice daily resulting in a daily dose of 800 mg for 8 weeks. Treatment duration may need to be individualised based on the clinical and virological characteristics of each patient.
LIVTENCITY is intended for oral use only and can be taken with or without food. The immediate release tablet can be taken as a whole tablet, a crushed tablet, or a crushed tablet through a nasogastric or orogastric tube

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	30 August 2021
Formal control completed	6 September 2021
List of Questions (LoQ)	28 April 2022
Response to LoQ	29 July 2022
2nd List of Questions (LoQ)	16 November 2022
Response to 2nd LoQ	24 November 2022
Preliminary decision	15 March 2023
Response to preliminary decision	11 May 2023
Final decision	19 July 2023
Decision	approval

3 Medical context

Cytomegalovirus (CMV) infection is caused by CMV, a member of the beta-herpes virus group. Primary CMV infection occurs in CMV seronegative hosts and is usually acquired during the first decades of life through sexual or close contact, from tissue or blood exposure, or perinatal exposure. Primary CMV infection is often symptomatic or mild and self-limited, but can be associated with increased morbidity and mortality in immunocompromised patients or newborns. CMV remains latent after primary infection, and intermittent viral shedding and disease reactivation can occur, particularly in immunocompromised individuals.

CMV is the most frequent opportunistic pathogen in transplant recipients, causing CMV infection, i.e. the presence of CMV replication in blood or tissues irrespective of signs or symptoms. This may progress to CMV disease, i.e. detectable CMV in blood or tissues accompanied by clinical symptoms or signs. CMV disease can manifest as end-organ disease or CMV syndrome. CMV syndrome occurs only in solid organ transplant (SOT) recipients and is characterised by detectable viral replication in blood with associated signs and symptoms such as fever, malaise, arthralgia, and leukopenia, without specific organ involvement.

The risk of CMV infection and disease in transplant recipients depends on transplant type, donor and recipient CMV serostatus, and the level of immunosuppression. In principle any organ can be infected and in SOT recipients the virus often replicates in the allograft. CMV infection is associated with an increased risk of other opportunistic infections, graft failure, graft rejection, and mortality.

At the time of the submission of the present application, there were no medicines approved in Switzerland for treatment of CMV infection and/or disease in either solid organ or stem cell transplant recipients, or for treatment of CMV in patients with resistant CMV.

Cytomegalovirus in Transplantation: Developing Drugs to Treat or Prevent Disease. Guidance for Industry. FDA, 2020

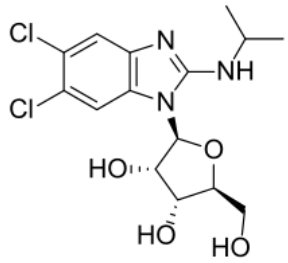
Santos CAQ, Vella J, Brennan DC. Clinical manifestations, diagnosis, and management of cytomegalovirus disease in kidney transplant patients. In: UpToDate, Legendre C, Blumberg EA (Eds), Wolters Kluwer (accessed December 2023)

Friel TJ. Epidemiology, clinical manifestations, and treatment of cytomegalovirus infection in immunocompetent adults. In: UpToDate, Hirsch MS (Ed), Wolters Kluwer (accessed December 2023)

4 Quality aspects

4.1 Drug substance

INN: Maribavir
Chemical name: 5,6-Dichloro-2-(isopropylamino)-1-β-L-ribofuranosyl-1H-benzimidazole
Molecular formula: $C_{15}H_{19}Cl_2N_3O_4$
Molecular mass: 376.24
Molecular structure:



Maribavir is a white to off-white solid. It shows pH-dependent solubility in aqueous solutions. Maribavir is classified as a Biopharmaceutics Classification System (BCS) Class 2 compound.

Maribavir has 4 stereocentres and is supplied as a single stereoisomer having an L-ribofuranosyl ring. Absolute stereochemistry is shown in the structural formula.

The drug substance is manufactured by multiple step chemical synthesis with final isolation by crystallisation and subsequent milling operation.

The drug substance specification includes relevant tests for proper quality control, encompassing e.g. tests relating to identification, assay, and related substances.

Appropriate stability data have been presented and justify the established re-test period.

4.2 Drug product

LIVTENCITY is an immediate release tablet for oral administration containing 200 mg maribavir. It is a blue, film-coated, oval-shaped convex tablet of 15.5 mm, debossed with “SHP” on one side and “620” on the other side.

The composition of the product is adequately described, qualitatively and quantitatively.

Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process.

The standard manufacturing process is described narratively and in sufficient detail, taking into account pharmaceutical development data, and including batch manufacturing formula and in-process controls.

The process performance qualification was successfully completed.

The drug product specification covers relevant physicochemical characteristics, as well as identification, assay, and purity tests. They allow for proper control of the drug product. The control methods are validated according to international guidelines. Batch data show consistent quality of the finished product.

The film-coated tablets are filled into a 60 mL white, square, high-density polyethylene bottle with a child-resistant closure.

Appropriate stability data have been generated for the drug product in the packaging material intended for marketing and following the relevant international guidelines. The data show good stability of the finished drug product and allow for a distinct assignment of the shelf life.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

5.1 Pharmacology

Maribavir's mechanism of action against human cytomegalovirus (HCMV) is through inhibition of the serine protein kinase UL97. In human lung fibroblast (MRC-5) cells infected with HCMV strain AD169 maribavir reduced the yield of infectious virus at 72 hours with an EC_{50} of 0.1 µM. Maribavir and all phosphorylated derivatives did not inhibit HCMV DNA polymerase at 100 µM.

The clinical assessor evaluated the studies on antiviral activity of maribavir and its major metabolite M4 as well as the assessment of resistance.

The cytotoxicity of maribavir was assessed in human marrow progenitor colony-forming units of granulocyte macrophages (CFU-GM) and burst-forming units-erythroid (BFU-E) cells and on rapidly dividing cells. Maribavir showed mean IC_{50} values of ~90 µM for CFU-GM and BFU-E and 35-76 µM on rapid dividing cells. These values are >12-fold higher than the maribavir concentration needed to inhibit 90% of the HCMV growth in MRC-5 cells. Therefore, the cytotoxic potential of maribavir is low.

Dedicated *in vivo* pharmacodynamics studies were not conducted as HCMV is specific for humans and therefore, animal models cannot be infected directly with HCMV.

Studies on secondary pharmacology showed no relevant effects.

The applicant conducted safety pharmacology studies to investigate potential effects on the cardiovascular, respiratory, and central nervous systems. Maribavir had no effect on the hERG current at concentrations up to 1500 µg/mL. Considering the levels of unbound drug at the clinical dose (C_{max} 0.34 µg/mL), it is unlikely that maribavir affects cardiac repolarisation. The *in vivo* studies were not conducted in compliance with GLP. However, they were accepted as the quality of the studies was considered adequate and electrocardiography assessment was conducted in the GLP-compliant repeat-dose toxicity studies in cynomolgus monkeys. In mice, moderate ataxia, tremors, diarrhoea, and decreased muscle tone were observed after single oral administration of 500 mg/kg. At ≥ 250 mg/kg, hypoactivity, hypothermia, blepharospasm, and variable effects on respiration were observed. Hypoactivity was also observed in single and repeat-dose toxicity studies in mice. However, these effects were not noted in monkeys in the repeat-dose toxicity study of up to 52 weeks duration. Fatigue was frequently observed in clinical studies.

Maribavir showed no inhibition of hERG-mediated potassium currents at concentrations 4000-fold the unbound human C_{max}. This safety margin does not indicate a concern for QT prolongation.

In dogs, a transient increase in heart rate and respiratory rate and volume, as well as a decrease in mean arterial pressure were observed after administration of 30 mg/kg. In repeat-dose toxicity studies of up to 52 weeks duration in cynomolgus monkeys, maribavir had no effect on electrocardiography parameters at doses up to 180 mg/kg/day.

5.2 Pharmacokinetics

The pharmacokinetics (PK) of maribavir were investigated after single intravenous and oral administration as well as after repeated oral administration in mice, rats, and cynomolgus monkeys. The PK profile of the metabolite M4 was studied in rats and monkeys after repeated oral administration.

Maribavir was rapidly absorbed in mice and rats after oral administration (T_{max} 0.5-0.6 hours), but more slowly in monkeys and humans (T_{max} 1 to 3 hours). The oral bioavailability differed consistently between mice (69%), rats (92% to 99%), and monkeys (42% to 112%).

Volume of distribution was high in all species studied (2.0 L/kg in mice, ≥1.6 L/kg in rats, and ≥5.7 L/kg in monkeys). Clearance was moderate to high (0.76–4.4 L/h/kg) in mice, rats, and monkeys. The terminal half-life in mice, rats, and monkeys was 1.18, 0.38, and 1.1 hours, respectively, and was shorter than that observed in humans (4.32 hours). In rats, rapid initial clearance (1.8 L/kg/h) followed by persistent systemic concentrations of maribavir was suggestive of enterohepatic circulation and

consistent with biliary excretion, which is the major route of clearance. In monkeys, clearance was approximately 0.8 L/kg/h with evidence of biliary recirculation, consistent with the data in rats.

In repeat-dose studies in mice, rats, and monkeys, exposure to maribavir increased in a generally dose-related manner. However, there was a trend towards a less-than-dose-proportional increase at higher doses.

There was minor accumulation in rats and monkeys. Sex-related differences in exposure to maribavir were observed in mice and rats, but not in monkeys. In mice, exposure was generally higher in males than females, whereas in rats, exposure was higher in females (approximately 2-fold) than males.

In a tissue distribution study with oral administration of 10 mg/kg ^{14}C-maribavir to pigmented and albino rats, drug-derived radioactivity was observed in most tissues. The kidneys, liver, and gastrointestinal tract had the highest concentrations of radioactivity. Based on the presence of drug-derived radioactivity in the uveal tract and pigmented skin, maribavir or metabolites show an affinity for melanin. Maribavir showed limited distribution to the central nervous system.

Maribavir binding was high in human plasma (98%) and somewhat lower in the nonclinical species plasma (84-88%). The protein binding of M4 in mouse, rat, rabbit, monkey, and human plasma was 76%, 71%, 91%, 78%, and 90%, respectively.

Maribavir showed some partitioning to red blood cells in rats, monkeys, and humans.

The metabolism of maribavir was examined *in vitro* in rat, monkey, and human liver microsomes. The primary metabolic pathways were oxidative N-dealkylation followed by glucuronidation, direct glucuronidation, and N-glycosidic hydrolysis. The metabolism of maribavir in human liver microsomes was mainly catalysed by CYP3A4 with the formation of M4 and to a minor extent by CYP1A2.

The excretion of ^{14}C-maribavir was investigated after intravenous and oral administration at 10 mg/kg in mice, rats, and monkeys. The major route of excretion in the nonclinical species was biliary and/or intestinal secretion into faeces, whereas in humans, excretion was mostly via urine.

Passage into milk and placental transfer were not investigated. The recommendation for breastfeeding in the information for healthcare professionals is adequate.

5.3 Toxicology

The nonclinical safety profile of maribavir was characterised in mice, rats, rabbits, guinea pigs, and cynomolgus monkeys. The oral route of administration as well as the duration of the studies in rodents and non-rodents support the clinical use. The toxicity of maribavir was evaluated in studies with daily dosing for up to 13 weeks in mice (50, 150, 300, or 500 mg/kg/day), 26 weeks in rats (25, 100, or 400 mg/kg/day with a recovery period of 4 weeks), and 52 weeks in monkeys (50, 100, or 200 mg/kg twice daily with a recovery period of 4 to 8 weeks).

The main target organs for toxicity were the haematopoietic and gastrointestinal systems.

The following findings were observed in all species investigated: regenerative anaemia, soft to liquid stool, electrolyte changes, and dehydration, associated with mucosal cell hyperplasia in the large and small intestine of mice and rats, and in the large intestine of monkeys. The findings were reversible or partially reversible.

A NOAEL could not be established in monkeys and was therefore considered to be <100 mg/kg/day. In mice and rats, the NOAELs were 150 mg/kg/day and 25 mg/kg/day, respectively. The exposures at the NOAELs were below the clinical exposure at the human recommended dose. The exposure of M4 relative to the NOAELs showed adequate coverage considering the free unbound exposures.

Maribavir was not genotoxic in an Ames assay at concentrations up to 650 µg/plate but demonstrated mutagenic potential in the absence of metabolic activation in the mouse lymphoma assay. However, it was not clastogenic in the *in vivo* micronucleus assay in rats after single oral administration of up to 1200 mg/kg (maximum tolerated dose) at an exposure 2.6-fold higher than the clinical exposure based on unbound C_{max}.

Maribavir was not carcinogenic in rats administered oral doses of up to 100 mg/kg/day for up to 104 weeks.

In mice, increased incidences of haemangioma, haemangiosarcoma, and combined hemangioma/haemangiosarcoma were observed in male animals at 150 mg/kg/day at exposures similar to the human clinical exposure. The relevance of these results to human is not clear.

A fertility and embryonic development study was conducted in male and female rats with oral administration of maribavir at doses up to 400 mg/kg/day. Maribavir decreased sperm velocity at all doses, but there were no effects on fertility or reproductive performance at any dose. In females, reduced embryofetal survival and increased pre- and post-implantation losses were observed at all doses at exposures approximately half the clinical exposure. Reduced body weight gain was observed in animals at ≥200 mg/kg/day.

Maribavir had no effect on embryo-fetal growth or development at dose levels up to 100 mg/kg/day in rabbits, at exposures similar to the clinical exposure.

In the pre- and postnatal developmental toxicity study in rats, a delay in developmental endpoints was observed in the offspring, including pinna detachment at ≥150 mg/kg/day, and eye opening and preputial separation associated with reduced bodyweight gain at 400 mg/kg/day. Decreased fetal survival and litter loss were observed due to maternal toxicity and poor maternal care at ≥150 mg/kg/day. No effects were observed at 50 mg/kg/day, which is estimated to be associated with an exposure below the clinical exposure. No effects on the number of offspring, proportion of males, number of live pups, or survival were observed at any dose in the offspring born in the second generation. The recommendation in the pregnancy section of the information for healthcare professionals is adequate.

In the juvenile toxicity study in rats with doses adjusted to maintain a steady exposure from postnatal day 7 to 34, (initial doses of 17 or 25 mg/kg/day in low- and high-dose groups in both female and male rats, up to 225 mg/kg/day in females and 300 mg/kg/day in males in the high-dose groups on post-natal day (PND) 34), there were no additional toxicity findings to those observed in adult animals.

Dedicated studies on immunotoxicity were not conducted. This is accepted, because there were no relevant findings in the general toxicity studies.

There are no concerns related to excipients or impurities.

Maribavir was not phototoxic *in vitro* in the neutral red uptake phototoxicity assay in BALB/c 3T3 mouse fibroblasts.

The summary of the key findings from the nonclinical studies in the RMP is acceptable. Overall, no safety risks were identified in the nonclinical studies that would require specific post-authorisation monitoring.

Based on the ERA, maribavir does not represent a risk for the environment at the prescribed dose.

5.4 Nonclinical conclusions

In conclusion, the pharmaco-toxicological profile of maribavir was well characterised. The application is approvable from the nonclinical perspective. The relevant information has been included in the information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

ADME

Absorption and biopharmaceutical development

The commercial formulation, an immediate release tablet containing 200 mg maribavir, was administered in the pivotal Phase 3 study SHP620-303.

The dosing recommendations regarding the intake of maribavir with or without food or as a crushed tablet included in the information for healthcare professionals were based on the similarity of the commercial tablet with other tablet formulations employed in the clinical development of maribavir.

Dose proportionality

After administration of single doses in the range of 50 mg to 1600 mg to healthy subjects or HIV patients, there was an approximately dose-proportional increase of maribavir C_{max} and AUC. After administration of multiple daily doses between 300 mg and 2400 mg as a BID or TID regimen to HIV patients, maribavir $AUC_{0\text{-}24,ss}$ increased approximately proportionally to the administered dose as well.

Pharmacokinetics after multiple dosing

After administration of multiple doses in the range of 100 mg to 400 mg TID and 600 mg to 1200 mg BID for 28 days to HIV patients, the linearity index was close to 1, indicating time-independent pharmacokinetics of maribavir. After both BID and TID dosing, there was an up to 1.5-fold accumulation. This is in agreement with the maribavir half-life of approximately 6 hours. Similar values were obtained in CMV patients. After 400 mg BID, 95% of the CMV patients included in the popPK analysis reached steady state after the fourth dose, i.e. after 2 days of BID dosing.

Distribution

The mean maribavir *in vitro* plasma protein binding was 98% and independent of the maribavir concentration (0.05 – 200 µg/mL). The majority of maribavir was bound to albumin *in vitro*.

The *ex vivo* plasma protein binding of maribavir was 98.7%. Renal impairment of all degrees as well as moderate hepatic impairment had no impact on *ex vivo* maribavir plasma protein binding.

The mean *in vitro* maribavir blood to plasma partitioning was 1.37, indicating a distribution into red blood cells.

The mean apparent volume of distribution at steady state of maribavir was estimated to be 27.3 L.

Metabolism - in vitro data

CYP3A4 was the main enzyme involved in the formation of VP 44469 (main metabolite of maribavir), with a minor contribution by CPY1A2.

UGT1A1, UGT1A3, and UGT2B7 – but not UGT1A4, UGT1A6, UGT1A10, or UGT2B15 – were also involved in the maribavir metabolism.

Metabolism & elimination - clinical data

After oral administration of a ^{14}C-labelled maribavir dose, maribavir and VP 44469 were the main analytes detected in plasma within 24 h postdose, accounting for all of the total radioactivity in plasma based on $AUC_{0\text{-}24h}$. VP 44469 is formed by N-dealkylation of maribavir, followed by glucuronide conjugation to yield M1; hydrolysis to loose ribose and subsequent formation of glucuronides M2 and M3; and oxidation of the isopropyl amine moiety to form metabolites M5 and M6.

After administration of single doses to healthy subjects, the metabolite/parent (MP) ratio based on AUC_{inf} for VP 44469 ranged from 15% to 20%. The pharmacological activity of VP 44469 is much lower compared to maribavir.

Less than 5% of the administered dose was excreted in urine as unchanged maribavir, while up to 42% of the maribavir dose was excreted as VP 44469 in urine in healthy subjects or HIV patients.

After oral administration of a ^{14}C-labelled maribavir dose, 61.2% and 13.6% of the radioactive dose was excreted in urine and faeces, respectively.

The most abundant metabolite excreted in urine was VP 44469, followed by M5 and M2. In faeces, only maribavir and VP 44469 were identified. The percentage of dose recovered in faeces as maribavir and VP 44469 was 5.7% and 7.2%, respectively.

Special populations

Mild to moderate or severe renal impairment had no major effect on maribavir exposures. The maximum change in maribavir exposures was a 1.67-fold increase of AUC_{inf} in subjects with mild renal impairment. There was no trend of increasing maribavir exposures with decreasing renal function.

There was a 1.35-fold and 1.26-fold increase in the total maribavir C_{max} and AUC_{inf} in subjects with moderate hepatic impairment (Child-Pugh B) compared to subjects with normal hepatic function. The increase in the unbound maribavir exposures was smaller. The maribavir half-life was prolonged to 8.05 h compared to 6.91 h.

Additional intrinsic factors including, but not limited to, age, weight gender, and health status were investigated in a popPK analysis. The popPK dataset included 9 Phase 1 studies, 2 Phase 2 studies, and the Phase 3 study SHP620-303. The dataset included 667 subjects, of which 485 (73%) were transplant patients with CMV and 133 (20%) healthy subjects. Hepatic and renal function were not assessed in the CMV patients, i.e. the only respective data came from the 2 dedicated Phase 1 studies. The overall age range of the subjects in the dataset was 18 to 79 years, with 119 subjects (18%) older than 65 years. Fifty-eight of these patients were included in study SHP620-303. The overall weight range of the subjects was 36.1 to 141 kg.

The final PK model was a 2-compartment model with first-order absorption and elimination, and an absorption lag-time. The model included CYP3A inhibitor and inducer effects on CL/F, dose effect on Ka, and CMV effect on CL/F. In addition, CL/F, Vc/F, Q/F, and Vp/F all increased with weight fixed to allometric scalars. Ka decreased with increasing maribavir dose. CL/F was estimated to be 30% lower in the presence of strong CYP3A inhibitors and 2.24-fold higher in the presence of strong CYP3A inducers, and 24% lower for transplant patients with CMV compared to all other subjects.

The model described the data sufficiently well to be suitable for simulations.

The estimated effects of intrinsic factors, including age, gender, body weight, and ethnic origin on maribavir (MAR) exposures were small with < 2-fold changes compared to the reference.

The data support the dosing recommendations described in the information for healthcare professionals.

Interactions

EFFECT OF OTHER DRUGS ON MARIBAVIR

In vitro data

As mentioned above, maribavir was mainly metabolised by CYP3A4. UGT1A1, UGT1A3, and UGT2B7 were also involved in the down-stream metabolism of maribavir. Maribavir was a substrate for the following transporters: P-gp, BCRP, and OCT1. It was not a substrate for OATP1B1, OATB1B3, or BSEP. No other transporters were investigated with regard to maribavir being a substrate.

Clinical data

Perpetrator	GMR (90% CI)
Ketoconazole (400 mg SD, strong CYP3A4 inhibitor, moderate CYP2C19 inhibitor, Pgp inhibitor)	**MAR**: C_{max}: 1.097 (1.013,1.188) AUCinf: 1.533 (1.444, 1.628)
Rifampicin (600 mg QD for 12 days, strong CYP & transporter inducer)	**MAR**: C_{max}: 0.612 (0.523, 0.717) AUC_{tlast}: 0.398 (0.361, 0.440) C_{trough}: 0.183 (0.135, 0.247)

GMR: geometric mean ratio

The inhibition of both CYP3A4 and Pgp had no major impact on maribavir exposures. The potential impact of BCRP or OCT1 inhibitors on maribavir exposures was not investigated, but the *in vivo* interaction risk appeared to be low.

PBPK simulations

The PBPK model to evaluate the interaction potential of maribavir as a victim was sufficiently qualified to be suitable for simulations. The results summarised in the table below refer to a maribavir dose of 400 mg BID.

Perpetrator	GMR
Phenobarbital	**MAR**: C_{max}: 0.72 AUC_{0-12h}: 0.60 C_{12h}: 0.31
Phenytoin	**MAR**: C_{max}: 0.68 AUC_{0-12h}: 0.57 C_{12h}: 0.30
Carbamazepine	**MAR**: C_{max}: 0.77 AUC_{0-12h}: 0.70 C_{12h}: 0.53
Efavirenz	**MAR**: C_{max}: 0.74 AUC_{0-12h}: 0.56 C_{12h}: 0.21
Ritonavir	**MAR**: C_{max}: 1.36 AUC_{0-12h}: 1.61 C_{12h}: 2.48
Diltiazem	**MAR**: C_{max}: 1.06 AUC_{0-12h}: 1.09 C_{12h}: 1.17
Erythromycin	**MAR**: C_{max}: 1.26 AUC_{0-12h}: 1.43 C_{12h}: 1.97

Apart from the evaluation of the impact of perpetrators not investigated, the PBPK model was also used to support dosing recommendations for the co-administration of perpetrators.

EFFECT OF MARIBAVIR ON OTHER DRUGS

In vitro data

Maribavir inhibited CYP1A2, 2C9 2C19, and 3A4 *in vitro*. An interaction risk at therapeutic exposures was identified for CYP1A2, 2C9, and 2C19.

Maribavir induced CYP3A4 with EC_{50} values between 4.9 and 17.9 µM. An *in vivo* induction of CYP1A2 cannot be excluded, while induction of CYP2B6 appears unlikely.

Maribavir inhibited UGT1A1, 1A3, 1A9, and 2B7. An interaction risk at therapeutic exposures could not be excluded for UGT1A3, 1A9, and 2B7.

Maribavir inhibited P-gp, BCRP, OATP1B1, OATP1B3, OAT3, MATE1, and BSEP. At the (sufficiently high) concentrations investigated, it did not inhibit OAT1, OCT1, OCT2, and MATE2K. An interaction at therapeutic exposures could not be excluded for OAT3, MATE2, intestinal Pgp, and BCRP, but no risk was identified for OATP1B1 or OATB1B3.

VP 44469 did not inhibit any of the CYPs investigated at concentrations up to 30 µM. Assuming an IC_{50} of 30 µM, the inhibition of CYP3A4 by VP 44469 at therapeutic exposures could not be excluded.

VP 44469 did not inhibit OAT1, OAT3, OCT2, MATE1, or MATE2K at concentrations up to 15.5 µM.

Clinical data

Victim	**GMR (90% CI)**
Caffeine (CYP1A2 substrate, cocktail)	**(1X+1U+AFMU)/17U:** 0.86 (0.80 - 0.92) **AFMU/(1X+1U):** 0.96 (0.86 - 1.06) **1U/(1X+1U):** 1.02 (1.00 - 1.04)
S-Warfarin (CYP2C9 substrate, cocktail)	AUC_{inf}: 1.01 (0.953 - 1.07)
Omeprazole (CYP2C19 substrate, cocktail)	Omeprazole/5-Hydroxyomeprazole Ratio: 1.71 (1.51 - 1.92)
Dextromethorphan (CYP2D6 substrate, cocktail)	Dextromethorphan/ Dextrorphan Ratio: 1.18 (0.95 - 1.41)
Dextromethorphan (CYP2D6 substrate)	**Dextromethorphan:** C_{max}: 0.939 (0.774, 1.139) AUC_{last}: 0.882 (0.696, 1.118) **Dextrorphan**: C_{max}. 0.943 (0.883, 1.007) AUC_{last}: 0.973 (0.949, 0.998) AUC_{inf}: 0.971 (0.943, 0.999) **Dextromethorphan/dextrorphan (parent/metabolite) ratio** AUC_{last}: 0.905 (0.721, 1.138)
Midazolam (CYP3A4 substrate, cocktail)	**Midazolam CL/F (mL/hr):** 1.13 (1.01 - 1.24) **1-Hydroxymidazolam AUC0-∞:** 1.06 (0.91 - 1.21)
Voriconazole (CYP2C19 substrate) Day – 1 vs Day 7	**VORI**: C_{max}: 0.996 (0.865, 1.147) AUC_{last}: 0.933 (0.830, 1.048) **N-OXIDE**: C_{max}: 1.005 (0.932, 1.084) AUC_{last}: 1.042 (0.992, 1.095) **Metabolite/parent ratio** AUC_{last}: 1.117 (1.019, 1.225)

	AUC_{inf}: 1.080 (0.893, 1.305)
Digoxin (Pgp substrate)	C_{max}: 1.257 (1.139, 1.387) AUC_{last}: 1.187 (1.088, 1.296) AUC_{inf}: 1.217 (1.110, 1.335)
Tacrolimus (CYP3A4 & Pgp substrate)	C_{max}: 1.376 (1.202, 1.574) AUC_{tau}: 1.511 (1.386, 1.648) C_{trough}, ss: 1.566 (1.409, 1.740)

Abbreviations from caffeine interaction study:
17U: 1,7-dimethylruic acid
AFMU: 5-acetylamino-6-formylamino-3-methyluracil
1X: 1-methylxanthine
1U: 1-dimethylruic acid

The effect of maribavir on caffeine and dextromethorphan was assessed by the measurement of the respective metabolites in urine, not by the plasma concentrations of the substrates. The only signal in this study was a possible inhibition of CYP2C19, which was not confirmed in the voriconazole interaction study.

The 90% CIs for digoxin were outside the pre-defined no-effect limits in study SHP620-115. These are too wide for (P-gp) substrates with a narrow therapeutic index. This was also the case for tacrolimus. A corresponding note was included in the information for healthcare professionals.

PBPK simulations

The PBPK model was sucessfully qualified by predicting the data of the digoxin interaction study. The model qualification and the simulations regarding the effect of maribavir on BCRP substrates used the original *in vitro* Ki values and substantially lower values. Furthermore, the simulations accounted for different BCRP phenotypes.

Victim	**GMR**
Sulfasalazine (Ki =0.23 µM)	C_{max}: 3.33 AUC_{inf}: 3.15
Sulfasalazine (Ki =0.062 µM)	C_{max}: 3.74 AUC_{inf}: 3.60
Rosuvastatin (Ki =0.23 µM), healthy subjects	C_{max}: 3.40 AUC_{inf}: 2.15
Rosuvastatin (Ki =0.062 µM), healthy subjects	C_{max}: 4.97 AUC_{inf}: 2.94
Rosuvastatin (Ki =0.23 µM), extensive BCRP transporters	C_{max}: 3.54 AUC_{inf}: 2.21
Rosuvastatin (Ki =0.062 µM), extensive BCRP transporters	C_{max}: 5.23 AUC_{inf}: 3.06
Rosuvastatin (Ki =0.23 µM), intermediate BCRP transporters	C_{max}: 2.84 AUC_{inf}: 1.88
Rosuvastatin (Ki =0.062 µM), intermediate BCRP transporters	C_{max}: 3.87 AUC_{inf}: 2.41
Rosuvastatin (Ki =0.23 µM), poor BCRP transporters	C_{max}: 2.12 AUC_{inf}: 1.54
Rosuvastatin (Ki =0.062 µM), poor BCRP transporters	C_{max}: 2.60 AUC_{inf}: 1.80

The clinical data and the PBPK simulations support the dosing recommendations presented in the information for healthcare professionals.

Pharmacodynamics

SECONDARY PHARMACOLOGY (SAFETY)

Maribavir did not cause a prolongation of ΔΔQTcI after administration of single doses of 100 mg and 1200 mg. Moxifloxacin had the expected effect, i.e. assay sensitivity was demonstrated. There was no statistically significant relationship between maribavir or VP 44469 plasma concentrations and ΔΔQTcI or ΔΔQTcF. Maribavir had no effect on heart rate at the concentrations investigated.

The tQT study was planned and conducted at the time when maribavir was being developed for the prevention of CMV infection, where the proposed therapeutic dose was 100 mg BID. The maribavir C_{max} after 400 mg BID is about 20 µg/mL. The maribavir C_{max} after the 1200 mg dose administered in study 1263-108 was 36.9 µg/mL. It can be concluded that maribavir did not cause QTc prolongations at therapeutic exposures after 400 mg BID, but no data are available for supratherapeutic exposures.

6.2 Dose finding and dose recommendation

The dose studied in the pivotal Phase 3 study was based on results from 2 Phase 2, multi-centre, randomised, dose-ranging studies. Study SHP620-202 evaluated the safety and anti-viral activity of maribavir in stem cell or solid organ transplant patients with CMV infections resistant or refractory to prior CMV treatment. Study SHP620-203 evaluated the safety and anti-viral activity of maribavir versus valganciclovir in stem cell or solid organ transplant patients with CMV infections without organ disease.

In study SHP620-202, participants were randomised 1:1:1 to receive maribavir administered orally at doses of 400 mg BID (n=40), 800 mg BID (n=40), or 1200 mg BID (n=40) for a maximum duration of 24 weeks.

In study SHP620-203, participants were randomised 1:1:1:1 to receive maribavir administered orally at doses of 400 mg BID (n=40), 800 mg BID (n=40), 1200 mg BID (n=40), or oral valganciclovir 900 mg BID (weeks 1-3) and 900 mg QD after Week 3 (n=40) for a maximum duration of 12 weeks.

In both studies, the participants and investigators were blinded to the maribavir dose.

Although there may be limited treatment options for these patients, the lack of an active control in study SHP620-202 hampers the interpretation of the results of the study. In particular, the safety data are difficult to interpret in view of the background disease and health status of the study population.

Valganciclovir as comparator in study SHP620-203 is acceptable, as oral valganciclovir or intravenous ganciclovir are the drugs of choice for treatment of CMV infections. Oral valganciclovir is also the drug of choice for pre-emptive treatment.

The primary efficacy endpoint in both studies was the proportion of patients with confirmed undetectable plasma CMV DNA (defined as 2 consecutive post-baseline, on-treatment plasma CMV DNA <200 copies/mL, results separated by at least 5 days) within 6 weeks (study SHP620-202) and within 3 weeks and 6 weeks (study SHP620-203). This endpoint is in line with recommendations in the FDA guidance.

Demographic and baseline characteristics were largely comparable across treatment groups in both studies. The study population included in study SHP620-202 was similar to that included in the pivotal Phase 3 study. Although allowed in study SHP620-202, no patients below 18 years of age were eventually included.

Overall, the dose-ranging studies confirm the antiviral activity of maribavir in the treatment of CMV infections in transplant recipients. For the primary efficacy endpoints, a numerical benefit of maribavir treatment (undetectable plasma CMV DNA at 3 weeks: 72/119 [60.5%] and 6 weeks: 92/119 [77.3%]) as compared to valganciclovir treatment (undetectable plasma CMV DNA at 3 weeks: 22/40 [55.0%] and 6 weeks: 26/40 [65.0%]) was observed in SHP620-203. No clear differences in response rates were observed between the various maribavir doses in any of the studies.

Regarding safety, the submitted data suggest a dose-response relation for specific AEs (dysgeusia, vomiting, diarrhoea), although this was not consistent in both studies. In particular, in study SHP620-

203, the highest maribavir dose seemed to be less well tolerated. The decision to further investigate the lowest maribavir dose studied (400 mg BID) in Phase 3 can therefore be endorsed.

The optimal treatment duration was discussed, as different treatment durations were investigated in the Phase 2 and 3 studies (SHP620-202: up to 24 weeks; SHP620-203: up to 12 weeks; SHP620-303: 8 weeks) and the majority of patients did not complete treatment. A treatment duration of 8 weeks that can be adjusted based on the clinical status of the patient was proposed, which is in line with the treatment duration in the pivotal study 303. As maintenance of the treatment effect through 16 weeks was low, prolonged treatment may be needed, depending on patients' immunosuppressive state.

6.3 Efficacy

Study SHP620-303 was a Phase 3, multi-centre, randomised, open-label, active-controlled study evaluating the efficacy and safety of maribavir compared to investigator-assigned anti-CMV treatment (IAT).

Recipients of stem cell or solid organ transplants aged 12 years or older with confirmed CMV infection that is refractory or resistant to treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir were eligible to participate. None of the enrolled participants was younger than 18 years.

The primary efficacy endpoint was confirmed clearance of plasma CMV DNA, defined as plasma CMV DNA concentrations <137 IU/mL (central laboratory) in 2 consecutive post-baseline samples separated by at least 5 days, at the end of study Week 8. The key secondary endpoint was achievement of CMV viraemia clearance and

- resolution or improvement of tissue-invasive disease or CMV syndrome (in those symptomatic at baseline), or
- no symptoms of tissue-invasive disease or CMV syndrome (in those asymptomatic at baseline)

at the end of study Week 8, followed by maintenance of this treatment effect for an additional 8 weeks off treatment.

These endpoints cover the elements recommended in the FDA guidance *Cytomegalovirus in Transplantation: Developing Drugs to Treat or Prevent Disease (FDA, CDER, 2020)* and are clinically relevant.

Participants were stratified by transplant type (stem cell transplant (SCT) or SOT) and by viral load level at screening (high, intermediate, low) and then randomised 2:1 to receive for a duration of 8 weeks:

- oral maribavir 400 mg BID (as two 200 mg tablets), or
- IAT: ganciclovir, valganciclovir, foscarnet, or cidofovir.

Subjects were not necessarily resistant or refractory to the IAT they received under the study protocol. However, it was shown that switching to a different IAT drug/regimen at randomisation had no impact on the outcome in the IAT arm.

Subjects in the IAT arm could enter a maribavir rescue arm if stringent criteria for lack of improvement/worsening of CMV infection were met following 3 weeks of treatment.

Subjects and investigators were unblinded to the treatment assignment. The choice of an open-label design is understood given the variability in the comparators (IAT) and their well-known adverse drug reactions. Furthermore, the virological primary endpoint is considered objective as it does not depend on investigators' assessments. Nevertheless, bias as a consequence of the open-label design cannot be ruled out, leaving uncertainty as to the exact treatment effect.

Results

Of 352 randomised patients, 220 (62.5%) completed 8 weeks of study-assigned treatment. The completion rate was higher in the maribavir group than in the IAT group (77.9% vs 31.6%, respectively), mainly driven by more frequent discontinuations due to AEs in the IAT group compared to the maribavir group (30.8% vs 6.4%, respectively).

Subject demographic and baseline characteristics were largely similar between the maribavir and IAT groups. Overall, 40% of subjects were SCT recipients and 60% SOT recipients. The majority of participants (>80%) had functioning transplants with no acute or chronic graft vs host disease.

Maribavir was superior to IAT in achieving confirmed CMV viraemia clearance at the end of Week 8 in transplant recipients with refractory CMV infection (with or without resistance): maribavir 55.7% and IAT 23.9% (p<.001). Analyses of the PP set and modified randomised set provided results similar to those of the randomised set. Based on the main reasons for treatment failure, the benefit of maribavir treatment may lie primarily in a better tolerability and not in a stronger antiviral effect.

The results of the sensitivity analyses are generally in line with those of the primary analysis, as a benefit of maribavir treatment was consistently seen across the different analyses. However, the sensitivity analyses confirm that part of the observed difference in CMV viraemia was due to a higher treatment discontinuation rate (possibly due to AEs, lack of efficacy, and/or subjects being aware of their treatment as a result of the open-label design) in the IAT group. The design of the study and the defined endpoint complicate a conclusion on the exact treatment effect of maribavir. However, this uncertainty can be accepted in view of the high medical need and the beneficial safety profile of maribavir.

Maribavir achieved favourable CMV viraemia clearance and CMV infection symptom control at Week 8, with maintenance of this treatment effect through to Week 16 (key secondary endpoint) compared with subjects in the IAT group (18.7% vs 10.3%, respectively; adjusted difference [95% CI] 9.5 [2.02, 16.88], p=.013).

CMV viraemia response following maribavir treatment was lower in patients with intermediate/high baseline viral load compared to those with low baseline viral load, while little difference between those subgroups was seen in the IAT group. In addition, lower CMV viraemia response in the maribavir group was seen in subjects who were refractory to treatment with (val)ganciclor, foscarnet, or cidofovir compared to subjects with genotypic resistance against those antivirals. In the IAT group, the reverse effect was seen, i.e. a lower response in those with genotypic resistance vs those refractory to treatment. These findings in the subgroups are described in the information for healthcare professionals.

6.4 Safety

A total of 680 subjects were exposed to maribavir in Phase 2 and 3 CMV studies and received maribavir doses of 100 mg BID, 400 mg QD, or 400 mg BID (200 mg/day to 800 mg/day) for 12 to 24 weeks. The pivotal study SHP620-303 provides the safety data most relevant to the target population. Study SHP620-202 and study SHP620-203 are considered supportive.

In study 303, the most frequently reported TEAEs (≥10%) during the on-treatment observation period in the maribavir group were dysgeusia (37%), nausea (21%), diarrhoea (19%), vomiting (14%), anaemia (12%), fatigue (12%), pyrexia (10%), and CMV viraemia (10%). The safety profile of maribavir administered in the rescue arm (i.e. after subjects received IAT in the IAT arm) was consistent with the data of the safety set for subjects initially randomised to maribavir.

Dysgeusia, nausea, vomiting, CMV infection and diarrhoea were also frequently reported with maribavir treatment in the Phase 2 studies 202 and 203. Dysgeusia and diarrhoea were reported more frequently with higher maribavir doses. The higher incidence of nausea, vomiting, diarrhoea, and rash observed in study 202 may result from longer exposure to maribavir in this study (up to 24 weeks of treatment) compared with studies 303 (8 weeks) and 203 (12 weeks).

The most frequently reported drug-related AEs in the maribavir group in study 303 were dysgeusia/taste disorder, vomiting, nausea, and immunosuppressant drug level increased. A warning is included in the information for healthcare professionals regarding the risk of increase in immunosuppressant drug levels and related toxicities. In the IAT group, the most frequently reported drug-related AEs were acute kidney disorder, anaemia, neutropenia, thrombocytopenia, and nausea.

Drug-related TEAEs lead to treatment discontinuation less frequently in the maribavir group compared to the IAT group (4.7% v. 23.3%). In the maribavir group, treatment discontinuation was mainly due to AEs in the SOC infections and infestations, while in the IAT group, AEs in the blood and lymphatic system disorders SOC (most often neutropenia) and renal and urinary disorders SOC (most often acute kidney injury) most frequently led to treatment discontinuation.

A total of 81 deaths were reported across the 3 studies: 40 (11.4%), 32 (26.7%), and 9 (5.6%) deaths in studies 303, 202, and 203, respectively. There were fewer deaths in study 203, mainly because the subjects were less ill (i.e. no invasive CMV and not resistant/refractory) than in the other 2 studies. The higher incidence of deaths in study 202 might be due to the potentially longer duration of treatment/follow-up compared to study 303.

In study 303, 38 patients experienced fatal SAEs with onset in the overall study observation period: 26 (11.1%) in the maribavir group and 12 (10.3%) in the IAT group. The most common SAEs leading to death were due to respiratory failure or relapse or progression of underlying disease. One fatal SAE in the maribavir group was potentially related to maribavir treatment (drug-drug interactions resulting in fatal arrhythmia).

Overall, across all studies, there was no notable pattern of fatal treatment-emergent SAEs within or between treatment groups.

6.5 Final clinical benefit-risk assessment

The applicant sought marketing authorisation for LIVTENCITY, containing the active substance maribavir, for the treatment of cytomegalovirus (CMV) infection.

Cytomegalovirus is the single most frequent opportunistic pathogen in transplant recipients.

Because of the increased morbidity and mortality associated with CMV disease in transplant recipients, treatment options for CMV infection and/or disease are needed.

At the time of the submission of this application, there were no medicines approved in Switzerland for treatment of CMV infection and/or disease in either solid organ or stem cell transplant recipients, or for treatment of CMV in patients with infection caused by resistant CMV.

Beneficial effects and respective uncertainties

The administration of maribavir as a crushed tablet, with a moderate-fat meal, or with an antacid had no clinically relevant effect on maribavir exposures. None of these evaluations used the market formulation. However, the risk of a significantly different behaviour of the market formulation appears to be low.

An evaluation of the effect of food on maribavir absorption according to the current regulatory guidelines (high-fat high calorie meal, final formulation) is missing. However, the commercial formulation was administered independently of food intake in the pivotal Phase 3 study.

The impact of proton pump inhibitors and histamine-2-receptor antagonists on maribavir absorption was investigated in a popPK analysis with sparse sampling only, which did not allow a proper characterisation of the absorption phase. The respective statement was removed from the information for healthcare professionals.

No formal evaluation of PK data after administration via a gastric tube is available. Only 1 patient in study SHP620-303 received maribavir crushed tablets via a gastric tube over a limited period of time.

Maribavir exposures increased proportionally to the administered doses in the relevant dose range. There was no evidence of time-dependent PK.

From a pharmacokinetic point of view, no dose adjustments for patients with renal impairment of all degrees or mild or moderate hepatic impairment are required.

Inhibitors of CYP3A4 and/or P-gp had no clinically relevant impact on maribavir exposures.

Maribavir did not cause QTc prolongations at therapeutic exposures. No data for supratherapeutic exposures are available.

The dose-ranging studies confirm the antiviral activity of maribavir in the treatment of CMV infections in transplant recipients and support the proposed maribavir dose of 400 mg BID. There was no clear difference in efficacy results across the various dosage groups, but safety data suggest a dose-response relationship for specific AEs. The efficacy and safety data from the Phase 3 study using the 400 mg BID dose further confirm the adequacy of this dose.

A benefit of maribavir treatment over IAT/standard of care in achieving confirmed CMV viraemia clearance in transplant recipients with CMV infection resistant/refractory to valganciclovir/ganciclovir, foscarnet, or cidofovir was demonstrated in 1 Phase 3 and an uncontrolled supportive Phase 2 study.

A double-blind controlled design for both studies would have been preferred. Bias as a result of the design cannot be ruled out. In addition, the efficacy and safety data from the Phase 2 study are difficult to interpret due to the lack of a control arm.

The benefit of maribavir in CMV viraemia clearance in the Phase 3 study seems to be impacted by more frequent treatment discontinuation (possibly due to AEs, lack of efficacy, and/or subjects being aware of their treatment as a result of the open-label design) in the IAT group. The results of various sensitivity analyses evaluating the impact of switching to alternative non-study anti-CMV drugs or maribavir rescue treatment, and premature study discontinuation consistently show a (numerical) benefit of maribavir. However, the design of the study and the defined endpoint complicate a conclusion on the exact treatment effect of maribavir. Its benefit may lie primarily in a better tolerability compared to currently available therapies.

Unfavourable effects and respective uncertainties

Dose adjustments are required for the co-administration of CYP inducers.

Maribavir as a perpetrator inhibits P-gp and BCRP. Consequently, monitoring and/or dose adjustments of respective substrates with a narrow therapeutic index are required. This is adequately reflected in the information for healthcare professionals. Some of the DDI studies investigating maribavir as a perpetrator were quite old and do not reflect the state of the art.

Maribavir treatment was generally well tolerated. The most frequently observed AEs are dysgeusia and gastrointestinal effects, which can be managed in clinical practice. A warning is included in the information for healthcare professionals regarding the risk of an increase in immunosuppressant drug levels and related toxicities. Maribavir seems to have a more favourable profile regarding bone marrow suppression and nephrotoxicity compared to other CMV treatments.

The safety database is limited and not sufficient to reliably capture less common adverse reactions. However, given the orphan status of maribavir in the requested indication, this can be considered acceptable.

Treatment-emergent resistance was observed following maribavir treatment. As some of the acquired mutations also confer resistance to valganciclovir/ganciclovir, maribavir should not be used as a first-line treatment.

Benefit-risk balance

The clinical pharmacology issues (among others, insufficient investigation of the enzymes involved in the metabolism of maribavir and the resulting limited evaluation of its interaction potential as a victim) were resolved or addressed in the information for healthcare professionals.

From a clinical point of view, the uncertainties on the exact treatment effect of maribavir can be accepted in view of the high medical need and maribavir’s observed favourable safety profile in comparison to other medicines used for the treatment of CMV infection/disease.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for LIVTENCITY was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

LIVTENCITY®

Composition

Active substances

Maribavir

Excipients

Microcrystalline cellulose (E460(i)), Sodium starch glycolate (Type A), Magnesium stearate (E470b), Polyvinyl alcohol (E1203), Macrogol 3350 (i.e. polyethylene glycol) (E1521), Titanium dioxide (E171), Talc (E553b), Brilliant blue FCF aluminum lake (E133)
Sodium content per film-coated tablet: 0.105 mg.

Pharmaceutical form and active substance quantity per unit

Film-coated tablets containing 200 mg maribavir.

Indications/Uses

LIVTENCITY is indicated for the treatment of cytomegalovirus (CMV) infection and/or disease that are refractory (with or without resistance) to one or more prior therapies, including ganciclovir, valganciclovir, cidofovir or foscarnet in adult patients who have undergone a haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT) (see section *Properties/Effects*).

Dosage/Administration

The recommended dose of LIVTENCITY is 400 mg (two 200 mg tablets) twice daily, resulting in a daily dose of 800 mg for 8 weeks. Treatment duration may need to be individualised based on the clinical and virological characteristics of each patient.

Special populations

Elderly patients

No dose adjustment is required for patients over 65 years (see sections *Properties/Effects* and *Pharmacokinetics*).

Renal impairment

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

Hepatic impairment

No dose adjustment of LIVTENCITY is needed for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. Administration of LIVTENCITY has not been studied in patients with severe hepatic impairment (Child-Pugh class C) (see section *Pharmacokinetics*).

Children and adolescents

LIVTENCITY is not authorised for use in the paediatric population.

Mode of administration

LIVTENCITY is intended for oral use only and can be taken with or without food. The immediate-release tablet can be taken as a whole tablet, a crushed tablet, or a crushed tablet through a nasogastric or orogastric tube.

Dose adjustment

Co-administration of LIVTENCITY with strong cytochrome P450 3A (CYP3A) inducers, such as rifampicin, rifabutin or St. John's wort, is not recommended due to the potential for a decrease in efficacy of maribavir. If LIVTENCITY is co-administered with other strong or moderate CYP3A inducers, the LIVTENCITY dose may need to be increased (see sections *Interactions* and *Pharmacokinetics*).

Missed dose

Patients should be instructed that if they miss a dose of LIVTENCITY, it is to be taken as soon as they remember. If they do not remember until it is time for the next dose, they should skip the missed dose and continue with the regular schedule. Patients should not double their next dose or take more than the prescribed dose.

Contraindications

Co-administration of LIVTENCITY with ganciclovir or valganciclovir (see section *Interactions*). Hypersensitivity to the active substance or to any of the excipients listed in section *Composition*.

Warnings and precautions

CMV disease with CNS involvement

LIVTENCITY has not been studied in patients with CMV infection with CNS involvement. Based on non-clinical data, maribavir may cross the blood-brain barrier in humans, but CNS penetration is expected to be low compared to plasma levels (see section *Preclinical data*). Therefore, LIVTENCITY is not expected to be effective in treating CMV infections with CNS involvement (e.g. meningo-encephalitis).

Virological failure during treatment and relapse post-treatment

Virological failure due to resistance can occur during and after treatment with LIVTENCITY. Virological relapse during the post-treatment period has 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.

Risk of adverse reactions or reduced therapeutic effect due to medicinal product interactions

The concomitant use of LIVTENCITY and certain medicinal products may result in known or potentially significant medicinal product interactions, some of which may lead to:

- possible clinically significant adverse reactions from greater exposure to concomitant medicinal products
- reduced therapeutic effect of LIVTENCITY.

See Table 1 for steps to prevent or manage these known or potentially significant medicinal product interactions, including dosing recommendations (see sections *Contraindication* and *Interactions*).

Use with immunosuppressant drugs

LIVTENCITY has the potential to increase the drug concentrations of immunosuppressant drugs that are cytochrome P450 (CYP)3A/P-gp substrates with narrow therapeutic ranges (including tacrolimus, ciclosporin, sirolimus and everolimus). The concentrations of immunosuppressant drugs must be frequently monitored throughout treatment with LIVTENCITY, especially following initiation and after discontinuation of LIVTENCITY; the dose should be adjusted, as needed (see sections *Interactions*, *Undesirable effects* and *Pharmacokinetics*).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

Interactions

Effect of other medicinal products on LIVTENCITY

Maribavir is primarily metabolised by CYP3A, and medicinal products that induce or inhibit CYP3A are expected to affect the clearance of maribavir (see section *Pharmacokinetics*).

Concomitant administration of strong CYP3A inducers, such as rifampicin, rifabutin, and St. John’s wort, should be avoided, as significant decreases may occur in plasma concentrations of maribavir, which may result in a decrease in efficacy. Alternative antimicrobial or anti-tuberculosis therapy, or anti-depressive therapy with a lower CYP3A induction potential, should be considered in this case (see section *Pharmacokinetics*).

Co-administration of LIVTENCITY with other strong or moderate CYP3A inducers has not been evaluated, but decreased maribavir concentrations are to be expected. If co-administration with other strong or moderate CYP3A inducers cannot be avoided, a LIVTENCITY dose increase as set out in Table 1 should be considered.

Co-administration of LIVTENCITY and medicinal products that are inhibitors of CYP3A may result in increased plasma concentrations of maribavir (see section *Interactions*). However, no dose adjustment is needed when maribavir is co-administered with CYP3A inhibitors.

Effect of LIVTENCITY on other medicinal products

LIVTENCITY is contraindicated with valganciclovir/ganciclovir. LIVTENCITY may antagonise the antiviral effect of ganciclovir and valganciclovir by inhibiting human CMV serine/threonine kinase UL97, which is required for activation/phosphorylation of ganciclovir and valganciclovir (see sections *Contraindications* and *Properties/Effects*).

At therapeutic concentrations, clinically significant interactions are not expected when LIVTENCITY is co-administered with substrates of 2A6, 2B6, 2C8, 2C9, 2C19, 2E1, 2D6, and 3A4; UGT1A1, 1A4, 1A6; bile salt export pump (BSEP); multidrug and toxin extrusion protein (MATE)2K; organic anion transporters (OAT)1; organic cation transporter (OCT)1 and OCT2; organic anion transporting polypeptide (OATP)1B1 and OATP1B3 based on *in vitro* studies and clinical drug interaction results (Table 1), except the following medicinal products.

In vitro, maribavir inhibits OAT3; therefore, plasma concentrations of medicinal products transported by OAT3 may be increased (e.g.: ciprofloxacin, imipenem, and cilastin).

In vitro, maribavir inhibits MATE1. There are no clinical data available on whether the co-administration of maribavir with sensitive MATE1 substrates (e.g. metformin) could potentially lead to clinically relevant interactions.

In vitro, maribavir induces CYP1A2. There are no clinical data available to estimate the risk of interaction due to CYP1A2 induction *in vivo*. The decrease in efficacy of sensitive CYP1A2 substrates such as tizanidine and theophylline cannot be excluded.

Co-administration of LIVTENCITY increased plasma concentrations of tacrolimus (see Table 1). When the immunosuppressants tacrolimus, ciclosporin, everolimus or sirolimus are co-administered with LIVTENCITY, immunosuppressant drug levels should be frequently monitored throughout treatment with LIVTENCITY, especially following initiation and after discontinuation of LIVTENCITY; the dose should be adjusted, as needed (see section *Undesirable effects* and Table 1).

Maribavir inhibited the P-gp transporter *in vitro* at clinically relevant concentrations. In a clinical study, co-administration of LIVTENCITY increased plasma concentrations of digoxin (see Table 1). Caution should be exercised when LIVTENCITY and sensitive P-gp substrates such as digoxin are

co-administered. Serum digoxin concentrations should be monitored, and the dose of digoxin may need to be reduced, as needed (see Table 1).

Co-administration of LIVTENCITY with rosuvastatin, a sensitive BCRP substrate, is expected to increase the rosuvastatin concentration. Rosuvastatin is associated with the occurrence of myopathy and rhabdomyolysis (see Table 1).

General information

If dose adjustments of concomitant medicinal products are made due to treatment with LIVTENCITY, the doses should be readjusted after treatment with LIVTENCITY is completed. Table 1 provides a list of known or potentially clinically significant medicinal product interactions. The medicinal product interactions described are based on studies conducted with LIVTENCITY or are predicted medicinal product interactions that may occur with LIVTENCITY (see section *Warnings and Precautions*).

Table 1: Interactions and dose recommendations for co-administration with other medicinal products

Medicinal product by therapeutic area	**Effect on geometric mean ratio (90% CI) (likely mechanism of action)**	**Recommendation concerning co-administration with maribavir**
Acid-reducing agents		
antacids (aluminium and magnesium hydroxide oral suspension) (20 mL single dose, maribavir 100 mg single dose)	↔ maribavir AUC 0.89 (0.83, 0.96) C_{max} 0.84 (0.75, 0.94)	No dose adjustment is required.
famotidine	Interaction not studied. Expected: ↔ maribavir	No dose adjustment is required.
omeprazole (40 mg single dose, maribavir 400 mg twice daily)	↔ maribavir ↑ plasma omeprazole/5-hydroxyomeprazole concentration ratio 1.71 (1.51, 1.92) 2 h after dosing (CYP2C19 inhibition)	No dose adjustment is required.
pantoprazole	Interaction not studied. Expected:	No dose adjustment is required.

Medicinal product by therapeutic area	Effect on geometric mean ratio (90% CI) (likely mechanism of action)	Recommendation concerning co-administration with maribavir
	pantoprazole ↑ (CYP2C19 inhibition) ↔ maribavir	
Antiarrhythmics		
digoxin (0.5 mg single dose, maribavir 400 mg twice daily)	↔ digoxin AUC 1.21 (1.10, 1.32) C_{max} 1.25 (1.13, 1.38) (P-gp inhibition)	Use caution when maribavir and digoxin are co-administered. Control levels of digoxin and monitor serum digoxin concentrations. The dose of sensitive P-gp substrates such as digoxin may need to be reduced when co-administered with maribavir.
Antibiotics		
erythromycin	Interaction not studied. Expected: ↑ maribavir (CYP3A inhibition)	No dose adjustment is required.
Anticonvulsants		
carbamazepine (400 mg single dose, maribavir 400 to 1200 mg twice daily)	PBPK simulations Maribavir 800 mg twice daily with carbamazepine versus maribavir 400 mg twice daily alone: AUC 1.40 (1.09, 1.67) C_{max} 1.53 (1.22, 1.79) C_{12h} 1.05 (0.71, 1.41) (CYP3A induction)	A dose adjustment of maribavir to 800 mg twice daily is recommended when co-administered with carbamazepine.

Medicinal product by therapeutic area	**Effect on geometric mean ratio (90% CI) (likely mechanism of action)**	**Recommendation concerning co-administration with maribavir**
phenobarbital (100 mg once daily, maribavir 400 to 1200 mg twice daily)	PBPK simulations Maribavir 1200 mg twice daily with phenobarbital versus maribavir 400 mg twice daily alone: AUC 1.80 (1.18, 2.35) C_{max} 2.17 (1.69, 2.57) C_{12h} 0.94 (0.22, 1.96) (CYP3A induction)	A dose adjustment of maribavir to 1200 mg twice daily is recommended when co-administered with phenobarbital.
phenytoin (300 mg once daily, maribavir 400 to 1200 mg twice daily)	PBPK simulation Maribavir 1200 mg twice daily with phenytoin versus maribavir 400 mg twice daily alone: AUC 1.70 (1.06, 2.46) C_{max} 2.05 (1.49, 2.63) C_{12h} 0.89 (0.26, 2.04) (CYP3A induction)	A dose adjustment of maribavir to 1200 mg twice daily is recommended when co-administered with phenytoin.
Anti-inflammatories		
sulfasalazine	Interaction not studied. Expected: ↑ sulfasalazine (BCRP inhibition)	No dose adjustment is required.
Antifungals		
ketoconazole (400 mg single dose, maribavir 400 mg single dose)	↑ maribavir AUC 1.53 (1.44, 1.63) C_{max} 1.10 (1.01, 1.19) (CYP3A and P-gp inhibition)	No dose adjustment is required.
voriconazole (200 mg twice daily, maribavir 400 mg twice daily)	Expected: ↑ maribavir (CYP3A inhibition)	No dose adjustment is required.

Medicinal product by therapeutic area	Effect on geometric mean ratio (90% CI) (likely mechanism of action)	Recommendation concerning co-administration with maribavir
	↔ voriconazole AUC 0.93 (0.83, 1.05) C_{max} 1.00 (0.87, 1.15) (CYP2C19 inhibition)	
Antihypertensives		
diltiazem	Interaction not studied. Expected: ↑ maribavir (CYP3A inhibition)	No dose adjustment is required.
Antimycobacterials		
rifabutin	Interaction not studied. Expected: ↓ maribavir (CYP3A induction)	Co-administration of maribavir and rifabutin is not recommended due to the potential for a decrease in efficacy of maribavir.
rifampin (600 mg once daily, maribavir 400 mg twice daily)	↓ maribavir AUC 0.40 (0.36, 0.44) C_{max} 0.61 (0.52, 0.72) C_{trough} 0.18 (0.14, 0.25) (CYP3A and CYP1A2 induction)	Co-administration of maribavir and rifampin is not recommended due to the potential for a decrease in efficacy of maribavir.
Antitussives		
dextromethorphan (30 mg single dose, maribavir 400 mg twice daily)	↔ dextrorphan AUC 0.97 (0.94, 1.00) C_{max} 0.94 (0.88, 1.01) (CYP2D6 inhibition)	No dose adjustment is required.
CNS stimulants		
Herbal products		

Medicinal product by therapeutic area	**Effect on geometric mean ratio (90% CI) (likely mechanism of action)**	**Recommendation concerning co-administration with maribavir**
St. John's wort (*Hypericum perforatum*)	Interaction not studied. Expected: ↓ maribavir (CYP3A induction)	Co-administration of maribavir and St. John's wort is not recommended due to the potential for a decrease in efficacy of maribavir.
HMG-CoA reductase inhibitors		
atorvastatin fluvastatin simvastatin	Interaction not studied. Expected: ↑ HMG-CoA reductase inhibitors	No dose adjustment is required.
rosuvastatin[a]	Interaction not studied. Expected: ↑ rosuvastatin (BCRP inhibition)	The patient should be closely monitored for rosuvastatin-related events, especially the occurrence of myopathy and rhabdomyolysis.
Immunosuppressants		
ciclosporin[a] everolimus[a] sirolimus[a]	Interaction not studied. Expected: ↑ ciclosporin, everolimus, sirolimus (CYP3A/P-gp inhibition)	Ciclosporin, everolimus and sirolimus levels should be frequently monitored, especially following initiation and after discontinuation of LIVTENCITY; the dose should be adjusted, as needed.
tacrolimus[a] (stable dose, twice daily, total daily dose range: 0.5-16 mg; maribavir 400 mg, twice daily)	↑ tacrolimus AUC 1.51 (1.39, 1.65) C_{max} 1.38 (1.20, 1.57) C_{trough} 1.57 (1.41, 1.74) (CYP3A/P-gp inhibition)	Tacrolimus levels should be frequently monitored, especially following initiation and after discontinuation of LIVTENCITY; the dose

Medicinal product by therapeutic area	**Effect on geometric mean ratio (90% CI) (likely mechanism of action)**	**Recommendation concerning co-administration with maribavir**
		should be adjusted, as needed.
Oral anticoagulants		
warfarin (10 mg single dose, maribavir 400 mg twice daily)	↔ S-warfarin AUC 1.01 (0.95, 1.07) (CYP2C9 inhibition)	No dose adjustment is required.
Oral contraceptives		
systemically acting oral contraceptive steroids	Interaction not studied. Expected: ↔ oral contraceptive steroids (CYP3A inhibition)	Maribavir can be used with oral contraceptives.
Sedatives		
midazolam (0.075 mg/kg oral single dose, maribavir 400 mg twice daily)	↔ midazolam AUC 0.89 (0.79, 1.00) C_{max} 0.82 (0.70, 0.96) (CYP3A inhibition)	No dose adjustment is required.

↑ = increase, ↓ = decrease, ↔ = no change

CI = Confidence Interval

*$AUC_{0-\infty}$ for single dose, AUC_{0-12} for twice daily dose.

Note: The table is not complete but provides examples of clinically relevant interactions.

[a] Refer to the respective prescribing information.

Children and adolescents

Interaction studies have only been performed in adults.

Pregnancy, lactation

Pregnancy

There are no data on maribavir use in pregnant women. Studies in animals have shown reproductive toxicity (see section *Preclinical data*). LIVTENCITY is not recommended during pregnancy and in

women of childbearing potential not using contraception. Women of childbearing potential should use reliable contraceptive methods during treatment.

Lactation

It is unknown whether maribavir or its metabolites are excreted in human milk. A risk to the breast-feeding child cannot be excluded. Breast-feeding should be discontinued during treatment with LIVTENCITY.

Fertility

Human fertility studies have not been conducted with LIVTENCITY. No effects on fertility were noted in rats in a combined fertility and embryofetal development study. At exposures below the human exposure at the recommended human dose [RHD], however, a decrease in straight-line sperm velocity was observed.
There were no effects on reproductive organs in either males or females in non-clinical studies in rats and monkeys (see section *Preclinical data*).

Effects on ability to drive and use machines

LIVTENCITY has no influence on the ability to drive and use machines.

Undesirable effects

Summary of the safety profile

The safety of LIVTENCITY was evaluated in Study 303, in which 352 patients were randomised and treated with LIVTENCITY (N=234) or investigator-assigned treatment consisting of monotherapy or dual therapy with ganciclovir, valganciclovir, foscarnet, or cidofovir (N=117) for 8 weeks following a diagnosis of resistant/refractory CMV infection. Adverse events that occurred during the treatment phase and follow-up phase through study week 20 were recorded. The mean exposure (SD) for LIVTENCITY was 48.6 (13.82) days. LIVTENCITY-treated patients received treatment for a maximum of 60 days.

The most commonly reported adverse reactions occurring in at least 10% of subjects in the LIVTENCITY group were: taste disturbance (46%), nausea (21%), diarrhoea (19%), vomiting (14%) and fatigue (12%). The most commonly reported serious adverse reactions were diarrhoea (2%) and nausea, weight decreased, fatigue, immunosuppressant drug concentration level increased, and vomiting occurring at > 1%.

List of adverse reactions

The following adverse reactions have been identified in patients taking LIVTENCITY in clinical trials. The adverse reactions are listed below by system organ class and frequency. Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) or very rare (< 1/10,000).

Adverse reactions identified with LIVTENCITY

Nervous system disorders

Very common: Taste disturbance (46.2%)[a]
Common: Headache

Gastrointestinal disorders

Very common: Diarrhoea (18.8%), Nausea (21.4%), Vomiting (14.1%)
Common: Abdominal pain upper

General disorders and administration site conditions

Very common: Fatigue (12.0%)
Common: Decreased appetite

Investigations

Common: Immunosuppressant drug level increased[b], weight decreased

[a] Taste disturbance includes the following reported preferred terms: ageusia, dysgeusia, hypogeusia and taste disorder.
[b] Immunosuppressant drug level increased includes the following reported preferred terms: immunosuppressant drug level increased and drug level increased.

Description of selected adverse reactions

Taste disturbance

Taste disturbance (comprised of the reported preferred terms ageusia, dysgeusia, hypogeusia and taste disorder) occurred in 46% of patients treated with LIVTENCITY. These events rarely led to discontinuation of LIVTENCITY (0.9%) and, for most patients, resolved while patients remained on therapy (37%) or within a median of 7 days (Kaplan-Meier estimate, 95% CI: 4-8 days) after treatment discontinuation.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no known specific antidote for maribavir. In the 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 maribavir, dialysis is unlikely to reduce plasma concentrations of maribavir significantly.

Properties/Effects

ATC code

J05AX10

Mechanism of action

The antiviral activity of maribavir is mediated by competitive inhibition of the protein kinase activity of HCMV enzyme UL97, which results in inhibition of protein phosphorylation.

Antiviral activity

Maribavir selectively inhibits *in vitro* HCMV replication in yield reduction, DNA hybridization, and plaque reduction assays in cell cultures at non-cytotoxic submicromolar concentrations. 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.

Combination antiviral activity

When maribavir was tested *in vitro* in combination with other antiviral compounds, it showed strong antagonism with ganciclovir and no antagonistic effect in combination with letermovir, foscarnet and cidofovir.

Viral resistance in cell culture

Maribavir does not affect UL54-encoded DNA polymerase, which, when presenting certain mutations, confers resistance to ganciclovir/valganciclovir, foscarnet and/or cidofovir. The following mutations conferring resistance to maribavir have been identified on the UL97 gene: L337M, F342Y, V353A, L397R, T409M, H411L/N/Y, and C480F. These mutations confer resistance that ranges from a 3.5-fold to > 200-fold increase in EC_{50} values. UL27 gene variants (R233S, W362R, W153R, L193F, A269T, V353E, L426F, E22stop, W362stop, 218delC, and 301-311del) conferred only mild maribavir resistance (< 5-fold increase in EC_{50}).

Viral resistance in clinical studies

In the Phase 2 Study 202 and Study 203 evaluating maribavir in 279 HSCT or solid organ transplant recipients, post-treatment pUL97 genotyping data from 23 of 29 patients who initially achieved viraemia clearance and later experienced recurrent CMV infection while on maribavir showed 17 patients with mutations T409M or H411Y and 6 patients with mutation C480F. Among 25 patients who did not respond to > 14 days of maribavir therapy, 9 had mutation T409M or H411Y, and 5 patients had mutation C480F. Additional pUL27 genotyping was performed on 39 patients in Study 202 and 43 patients in Study 203. The only resistance-associated amino acid substitution in pUL27 that was not detected at baseline was G344D. Phenotypic analysis of pUL27 and pUL97 recombinants showed

that pUL97 mutations T409M, H411Y, and C480F conferred 78-fold, 15-fold, and 224-fold increases, respectively, in maribavir EC_{50} compared with the wild-type strain. The pUL27 mutation G344D was not shown to confer maribavir resistance.

In the 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 60 subjects and were associated with non-response (47 subjects were on-treatment failures and 13 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. In addition, the following multiple mutations were associated with non-response: F342Y+T409M+H411N (78-fold), C480F+H411L+H411Y (224-fold), F342Y+H411Y (56-fold), T409M+C480F (224-fold) and H411Y+C480F (224-fold).

Cross-resistance

Cross-resistance has been observed between maribavir and ganciclovir/valganciclovir (vGCV/GCV) in cell cultures and in clinical studies. In the Phase 3 Study 303, a total of 44 patients in the maribavir arm had a treatment-emergent resistance-associated substitution (RAS) after investigator-assigned anti-CMV treatment (IAT). Of these, 24 had treatment-emergent C480F or F342Y RAS, both of which are cross-resistant to both ganciclovir/valganciclovir and maribavir. Of these 24 patients, 1 (0.04%) achieved the primary endpoint. Overall, only eight of these 44 patients achieved the primary endpoint. pUL97 vGCV/GCV resistance-associated substitutions F342S/Y, K355del, V356G, D456N, V466G, C480R, P521L, and Y617del reduce susceptibility to maribavir by > 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.

The pUL97 F342Y and C480F substitutions are maribavir treatment-emergent resistance-associated substitutions that confer a > 1.5-fold reduction in susceptibility to vGCV/GCV 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. The 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 pUL27 substitutions in these drugs, cross-resistance is not expected for pUL27 maribavir substitutions.

Pharmacodynamics

Cardiac electrophysiology

The effect of maribavir on the QTc interval at doses up to 1200 mg was evaluated in a randomised, single-dose, placebo-and active-controlled (moxifloxacin 400 mg oral) 4-period crossover thorough QT trial in 52 healthy subjects. Maribavir did not prolong the QTc interval to any clinically relevant extent following the 1200 mg dose, with peak plasma concentrations approximately twice the steady-state peak concentration following 400 mg twice daily doses in transplant patients.

Clinical efficacy

LIVTENCITY was evaluated in a Phase 3, multi-centre, randomised, open-label, active-controlled superiority study (Study SHP620-303) to assess the efficacy and safety of LIVTENCITY treatment compared to investigator-assigned treatment in 352 HSCT and solid organ transplant 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 anti-CMV agents. Patients were stratified by transplant type (HSCT or solid organ transplant) and viral load at screening and then randomised in a 2:1 allocation ratio to receive LIVTENCITY 400 mg twice daily or investigator-assigned treatment (ganciclovir, valganciclovir, foscarnet, or cidofovir) for an 8-week treatment period and 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. Baseline disease characteristics are summarised in Table 2 below.

Table 2: Summary of the baseline disease characteristics of the study population in Study 303.

Characteristic[a]	**Investigator-assigned treatment** **(N = 117)**	**LIVTENCITY 400 mg twice daily** **(N = 235)**
Investigator-assigned treatment		
Foscarnet	47 (41)	n/a
Ganciclovir/Valganciclovir	56 (48)	n/a
Cidofovir	6 (5)	n/a
Foscarnet+Ganciclovir/Valganciclovir	7 (6)	n/a
Transplant type, n (%)		
HSCT	48 (41)	93 (40)
Solid organ transplant[b]	69 (59)	142 (60)
Kidney[e]	32 (46)	74 (52)

Lung[e]	22 (32)	40 (28)
Heart[e]	9 (13)	14 (10)
Multiple[e]	5 (7)	5 (4)
Liver[e]	1 (1)	6 (4)
Pancreas[e]	0	2 (1)
Intestine[e]	0	1 (1)
CMV DNA levels category as reported by central laboratory, n (%)[c]		
High	7 (6)	14 (6)
Intermediate	25 (21)	68 (29)
Low	85 (73)	153 (65)
Baseline symptomatic CMV infection[d]		
No	109 (93)	214 (91)
Yes[d]	8 (7)	21 (9)
CMV syndrome (solid organ transplant only), n (%)[d, e, f]	7 (88)	10 (48)
Tissue-invasive disease, n (%)[d, e, f]	1 (13)	12 (57)

CMV=cytomegalovirus, DNA=deoxyribonucleic acid, HSCT=haematopoietic stem cell transplant, max=maximum, min=minimum, N=number of patients.

[a] Baseline was defined as the last value on or before the day of the first dose of study-assigned treatment, or date of randomisation for patients who did not receive study-assigned treatment.

[b] The most recent transplant.

[c] Viral load was defined for analysis by the baseline central specialty laboratory plasma CMV DNA qPCR results as *high* (≥ 91,000 IU/mL), *intermediate* (≥ 9,100 and < 91,000 IU/mL), and *low* (< 9,100 IU/mL).

[d] Confirmed by the Endpoint Adjudication Committee (EAC).

[e] Percentages are based on the number of patients within the category.

[f] Patients could have CMV syndrome and tissue-invasive disease.

The primary efficacy endpoint was confirmed CMV viraemia clearance (plasma CMV DNA concentration below the lower limit of quantification, i.e. < 137 IU/mL) at week 8. The key secondary endpoint was CMV viraemia clearance and CMV infection symptom control at week 8 with maintenance of this treatment effect through study week 16.

Table 3: Primary and key secondary efficacy endpoint analysis (randomised set) in Study 303

	Investigator-assigned treatment (N=117)	**LIVTENCITY 400 mg twice daily (N=235)**

	n (%)	n (%)
Primary endpoint: CMV viraemia clearance response at week 8		
Overall		
Responders	28 (24)	131 (56)
Adjusted difference in proportion of responders (95% CI)[a]		32.8 (22.8, 42.7)
p-value: adjusted[a]		< 0.001
Key secondary endpoint: Achievement of CMV viremia clearance and CMV infection symptom control[b] at week 8, with maintenance through week 16[b]		
Overall		
Responders	12 (10)	44 (19)
Adjusted difference in proportion of responders (95% CI)[a]		9.45 (2.0, 16.9)
p-value: adjusted[a]		0.013

CI=confidence interval; CMV=cytomegalovirus; N=number of patients.

[a] The Cochran-Mantel-Haenszel weighted average test was used for the adjusted difference in proportions (on maribavir and investigator-assigned treatment), the corresponding 95% CI, and the p-value after adjusting for the transplant type and baseline plasma CMV DNA concentration.

[b] 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.

The reasons for failure to meet the primary endpoint are summarised in Table 4.

Table 4: Analysis of failures for primary efficacy endpoint

Outcome at week 8	**Investigator-assigned treatment N=117 n (%)**	**LIVTENCITY N=235 n (%)**
Responders (confirmed DNA level < LLOQ)[a]	**28 (24)**	**131 (56)**
Non-responders:	**89 (76)**	**104 (44)**
Due to virological failure:	**42 (36)**	**80 (34)**
• CMV DNA never < LLOQ	35 (30)	48 (20)
• CMV DNA breakthrough[b]	7 (6)	32 (14)
Due to drug/study discontinuation:	**44 (38)**	**21 (9)**
• Adverse events	26 (22)	8 (3)
• Deaths	3 (3)	10 (4)
• Withdrawal of consent	9 (8)	1 (<1)
• Other reasons[c]	6 (5)	2 (1)

Due to other reasons but remained on study[d]	**3 (3)**	**3 (1)**

CMV=cytomegalovirus, DNA=deoxyribonucleic acid, LLOQ= lower limit of quantification, N=number of patients.

Percentages are based on the number of subjects in the randomised 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 withdrawal of consent, e.g. lack of efficacy and non-compliance.

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

The treatment effect was consistent across key subgroups and supports the generalisability of the study outcomes (see Table 5).

Table 5: Percentage of responders by subgroup in Study 303

	Investigator-assigned treatment (N = 117)		**LIVTENCITY 400 mg twice daily (N = 235)**	
	n/N	**%**	**n/N**	**%**
Transplant type				
Solid organ transplant	18/69	26	79/142	56
HSCT	10/48	21	52/93	56
Baseline CMV DNA viral load				
Low	21/85	25	95/153	62
Intermediate/high	7/32	22	36/82	44
Genotypic resistance to other anti-CMV agents				
Yes	14/69	20	76/121	63
No	11/34	32	42/96	44
CMV syndrome/disease at baseline				
Yes	1/8	13	10/21	48
No	27/109	25	121/214	57
Age group				
18 to 44 years	8/32	25	28/55	51
45 to 64 years	19/69	28	71/126	56
≥ 65 years	1/16	6	32/54	59

CMV=cytomegalovirus, DNA=deoxyribonucleic acid, HSCT=haematopoietic stem cell transplant.

Recurrence

Recurrence requiring anti-CMV treatment after week 8 was reported for 34/131 (26.0%) patients on LIVTENCITY compared to 10/28 (35.7%) patients on investigator-assigned treatment. The median time to recurrence after CMV viraemia clearance was 21 days (range 13 to 80) in the LIVTENCITY group and 22 days (range 14 to 36) in the investigator-assigned treatment group.

Rescue arm

Twenty-two patients received LIVTENCITY as rescue therapy due to worsening of CMV viraemia or new/persistent symptomatic CMV infections (7 patients, 31.8%) or lack of improvement in CMV infection plus intolerance to investigator-assigned treatment (15 patients, 68.2%). Of the 22 patients, 11 (50.0%) patients achieved confirmed CMV viraemia clearance at week 8 of the LIVTENCITY rescue treatment phase and 11 (50.0%) patients were non-responders.

Overall, the favourable results observed in Study 303 were consistent with the results from the Phase 2 studies; thus, these earlier studies provide further support for the use of LIVTENCITY in the treatment of post-transplant CMV infection and disease in adults.

Children and adolescents

The European Medicines Agency has deferred the obligation to submit the results of studies with LIVTENCITY in one or more subsets of the paediatric population for treatment of cytomegalovirus infection (see section *Dosage/Administration*).

Pharmacokinetics

Absorption

Maribavir pharmacological activity is due to the parent drug. The pharmacokinetics of maribavir have been characterised following oral administration in healthy subjects and transplant recipients. Maribavir exposure increased approximately dose-proportionally. In healthy subjects, the estimated geometric mean values in a population pharmacokinetic analysis for steady-state $AUC_{0-\tau}$, C_{max} and C_{trough} were 101 µg*h/mL, 16.4 µg/mL and 2.89 µg/mL, respectively, following 400 mg twice daily oral administration of maribavir.
In transplant recipients, maribavir steady-state exposure following oral administration of 400 mg twice daily is presented below, based on a population pharmacokinetic analysis. Steady state was reached in 2 days, with an accumulation ratio of 1.47 for AUC and 1.37 for C_{max}.

Table 6: Maribavir pharmacokinetic properties based on a population pharmacokinetic analysis

Parameter GM (% CV)	$AUC_{0-\tau}$ µg*h/mL	C_{max} µg/mL	C_{trough} µg/mL
Maribavir 400 mg twice daily	128 (50.7%)	17.2 (39.3%)	4.90 (89.7%)

GM: geometric mean, % CV: Geometric coefficient of variation

Maribavir was rapidly absorbed with peak plasma concentrations occurring 1.0 to 3.0 hours post-dose. Exposure to maribavir is unaffected by crushing the tablet, administration of a crushed tablet through a nasogastric or orogastric tube, or antacids.
Intrasubject variability (< 22%) and intersubject variability (< 37%) in maribavir PK parameters are low to moderate.

Effect of food

In healthy subjects, oral administration of a single 400 mg dose of maribavir with a moderately high-fat meal did not have any statistically significant effect on the overall exposure (AUC) and resulted in a 28% decrease in the C_{max} of maribavir. Maribavir can be administered orally with or without food, as has been the case in the clinical studies.

Distribution

Based on population pharmacokinetic analyses, the mean apparent steady-state volume of distribution is estimated to be 27.3 L.
In vitro binding of maribavir to human plasma proteins is 98.0% over the concentration range of 0.05-200 µg/mL. *Ex vivo* protein binding of maribavir (98.5%-99.0%) is consistent with the *in vitro* data, with no apparent difference observed among healthy subjects, subjects with (moderate) hepatic or (mild, moderate, or severe) renal impairment, patients infected with the human immunodeficiency virus (HIV), or transplant recipients.
Maribavir can penetrate the blood-retinal barrier and may cross the blood-brain barrier in humans based on the results from non-clinical studies, but CNS penetration is expected to be low compared to plasma levels.

Metabolism

Maribavir is primarily metabolised in the liver by CYP3A4 (primary metabolic pathway; fraction metabolised estimated to be at least 35%), and to a lesser extent by CYP1A2 (fraction metabolised estimated to be no more than 25%). The major metabolite of maribavir is formed by N-dealkylation of the isopropyl moiety and is considered pharmacologically inactive. The ratio of metabolite to parent compound for this major metabolite in plasma was 0.15-0.20.
According to *in vitro* studies, metabolism of maribavir is not mediated by CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A5, UGT1A4, UGT1A6, UGT1A10, or UGT2B15. Multiple UGT enzymes, namely UGT1A1, UGT1A3, UGT2B7, and possibly UGT1A9, are involved in the glucuronidation of maribavir in humans. However, the contribution of glucuronidation to the overall clearance of maribavir is low based on *in vitro* data.

Elimination

In transplant recipients, the mean oral clearance of maribavir is 2.85 L/h; the mean half-life observed during twice-daily dosing is 4.32 hours, and the mean terminal elimination half-life is 11.8 hours (the latter determined by population PK analysis). After single dose oral administration of [^{14}C]-maribavir, approximately 61% and 14% of the radioactivity were recovered in urine and faeces, respectively, primarily as the inactive major metabolite. Urinary excretion of unchanged maribavir is minimal.

Kinetics in specific patient groups

Renal impairment

No clinically significant impact of mild (estimated glomerular filtration rate [eGFR] between 60 and 89 mL/min), moderate (eGFR between 30 and 59 mL/min) or severe (eGFR less than 30 mL/min) renal impairment on maribavir total PK parameters was observed following a single dose of 400 mg maribavir. The maximum increase in the maribavir AUC between patients with mild/moderate or severe renal impairment and subjects with normal renal function was ≤ 67%.

Hepatic impairment

No clinically significant impact of moderate hepatic impairment (Child-Pugh class B, score of 7-9) on total unbound maribavir PK parameters was observed following a single dose of 200 mg maribavir. Compared to the healthy control subjects, AUC and C_{max} were 26% and 35% higher, respectively, in patients with moderate hepatic impairment.

Age, gender, race, ethnicity, and weight

Age (18-79 years), gender, race (Caucasian, Black, Asian, or others), ethnicity (Hispanic/Latino or non-Hispanic/Latino) and body weight (36 to 141 kg) did not have a clinically significant impact on the pharmacokinetics of maribavir, based on a population pharmacokinetic analysis.

Transplant types

Transplant types (HSCT vs. solid organ transplant), the type of solid organ transplant (liver, lung, kidney, or heart) or the presence of gastrointestinal graft-versus-host disease (GvHD, n=12) do not have a clinically significant impact on the pharmacokinetics of maribavir.

Preclinical data

Safety pharmacology

In safety pharmacology studies, maribavir had no major effects on the CNS, cardiovascular or respiratory systems, or autonomic functions.

Long-term toxicity

Regenerative anaemia and mucosal cell hyperplasia in the intestinal tract, together with dehydration, were observed in mice, rats and monkeys, accompanied by clinical observations of soft to liquid stool,

and electrolyte changes. Exposure at the NOAEL (no observed adverse effect level) in the investigated species was below the exposure at the RHD.
LIVTENCITY did not demonstrate phototoxicity *in vitro*.

Carcinogenicity

Maribavir is not carcinogenic in rats at doses up to 100 mg/kg/day. However, exposure was lower than human exposure at the RHD. In male mice, an elevation in the incidence of haemangioma, haemangiosarcoma, and combined haemangioma/haemangiosarcoma across multiple tissues was noted at 150 mg/kg/day. The translation of this to human risk is uncertain, given the lack of an effect in female mice or rats after 104 weeks of administration, the lack of neoplastic proliferative effects in male and female mice after 13 weeks of administration, the negative genotoxicity package and the difference in duration of administration in humans. There were no carcinogenic findings at a dose of 75 mg/kg/day. Exposure at this dose was lower than exposure at the RHD.

Mutagenicity

Maribavir was not mutagenic in a bacterial mutation assay and not clastogenic in the bone marrow micronucleus assay. In mouse lymphoma assays, maribavir demonstrated mutagenic potential in the absence of metabolic activation and the results were equivocal in the presence of metabolic activation. Overall, the weight of evidence indicates that maribavir does not exhibit genotoxic potential.

Reproductive toxicity

In the combined fertility and embryofoetal development study in rats, maribavir did not show any effects on fertility. However, in male rats decreases in sperm straight line velocity were observed at doses ≥ 100 mg/kg/day (at exposure lower than exposure at the RHD).
Fertility and mating performance of offspring, and their ability to maintain pregnancy and to deliver live offspring, were unaffected by maribavir in the pre- and post-natal development study in rats at doses up to 400 mg/kg/day.
In a combined fertility and embryofoetal development study in rats, maribavir had no effect on embryofoetal growth or development at doses up to 400 mg/kg/day. A decrease in the number of viable foetuses and an increase in early resorptions and post-implantation losses were observed only at maternally toxic doses of ≥100 mg/kg/day (exposure which is approximately half the human exposure at the RHD).
In the pre- and post-natal developmental toxicity study, decreased pup survival occurred due to poor maternal care and reduced body weight gain associated with a delay in developmental endpoints (pinna detachment, eye opening and preputial separation) at doses ≥ 150 mg/kg/day. No findings were observed at 50 mg/kg/day (exposure lower than human exposure at the RHD).
In rabbits, maribavir has no effects on embryofoetal growth or embryofoetal development at doses up to 100 mg/kg/day (exposure lower than human exposure at the RHD).

Juvenile toxicity

No new toxicity findings were identified in juvenile rats at doses up to 100 mg/kg/day.

Other information

Incompatibilities

Not applicable.

Effects on diagnostic methods

Not applicable.

Shelf life

LIVTENCITY can be used until the expiry date stated on the label and carton under "EXP". This medicinal product must not be used after the expiry date.

Special precautions for storage

Do not store above 30°C.
Store in the original packaging. Keep the medicine out of the reach of children.

Instructions for handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

68492 (Swissmedic)

Packs

Packs of 28 or 56 film-coated tablets (A).

Marketing authorisation holder

Takeda Pharma AG, 8152 Opfikon

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