

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

▼ 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 adverse reactions. See section 4.8 for how to report adverse reactions.

## **1. NAME OF THE MEDICINAL PRODUCT**

LIVTENCITY 200 mg film-coated tablets.

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 200 mg maribavir.

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Film-coated tablet.

Blue, oval shaped convex tablet of 15.5 mm, debossed with “SHP” on one side and “620” on the other side.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

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).

Consideration should be given to official guidance on the appropriate use of antiviral agents.

### **4.2 Posology and method of administration**

LIVTENCITY should be initiated by a physician experienced in the management of patients who have undergone solid organ transplant or haematopoietic stem cell transplant.

#### Posology

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 characteristics of each patient.

### Co-administration with CYP3A inducers

Co-administration of LIVTENCITY with the strong cytochrome P450 3A (CYP3A) inducers rifampicin, rifabutin or St. John's wort is not recommended due to potential for a decrease in efficacy of maribavir.

If co-administration of LIVTENCITY with other strong or moderate CYP3A inducers (e.g., carbamazepine, efavirenz, phenobarbital and phenytoin) cannot be avoided, the LIVTENCITY dose should be increased to 1 200 mg twice daily (see sections 4.4, 4.5 and 5.2).

### Missed dose

Patients should be instructed that if they miss a dose of LIVTENCITY, and the next dose is due within the next 3 hours, 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.

### Special populations

#### *Elderly patients*

No dose adjustment is required for patients over 65 years (see sections 5.1 and 5.2).

#### *Renal impairment*

No dose adjustment of LIVTENCITY is required for patients with mild, moderate or severe renal impairment. Administration of LIVTENCITY in patients with end stage renal disease (ESRD), including patients on dialysis, has not been studied. No dose adjustments is expected to be required for patients on dialysis due to the high plasma protein binding of maribavir (see section 5.2).

#### *Hepatic impairment*

No dose adjustment of LIVTENCITY is required for patients with mild (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B). Administration of LIVTENCITY in patients with severe hepatic impairment (Child-Pugh Class C) has not been studied. It is not known whether exposure to maribavir will significantly increase in patients with severe hepatic impairment. Therefore, caution is advised when LIVTENCITY is administered to patients with severe hepatic impairment (see section 5.2).

#### *Paediatric population*

The safety and efficacy of LIVTENCITY in patients below 18 years of age have not been established. No data are available.

### Method of administration

Oral use.

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

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Co-administration with ganciclovir or valganciclovir (see section 4.5).

#### **4.4 Special warnings and precautions for use**

##### Virologic failure during treatment and relapse post-treatment

Virologic failure can occur during and after treatment with LIVTENCITY. Virologic relapse during the post-treatment period usually occurred within 4-8 weeks after treatment discontinuation. Some maribavir pUL97 resistance-associated substitutions confer cross-resistance to ganciclovir and valganciclovir. CMV DNA levels should be monitored and resistance mutations should be investigated in patients who do not respond to treatment. Treatment should be discontinued if maribavir resistance mutations are detected.

##### CMV disease with CNS involvement

LIVTENCITY was not studied in patients with CMV CNS infection. Based on nonclinical data, CNS penetration of maribavir is expected to be low compared to plasma levels (section 5.2 and 5.3). Therefore, LIVTENCITY is not expected to be effective in treating CMV CNS infections (e.g. meningo-encephalitis).

##### Use with immunosuppressants

LIVTENCITY has the potential to increase the concentrations of immunosuppressants that are cytochrome P450 (CYP)3A/P-gp substrates with narrow therapeutic margins (including tacrolimus, cyclosporine, sirolimus and everolimus). The plasma levels of these immunosuppressants must be frequently monitored throughout treatment with LIVTENCITY, especially following initiation and after discontinuation of LIVTENCITY, and doses should be adjusted, as needed (see sections 4.5, 4.8 and 5.2).

##### 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 of 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 4.3 and 4.5).

##### Sodium content

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

#### **4.5 Interaction with other medicinal products and other forms of interaction**

##### Effect of other medicinal products on maribavir

Maribavir is primarily metabolised by CYP3A, and medicinal products that induce or inhibit CYP3A are expected to affect the clearance of maribavir (see section 5.2).

Co-administration of maribavir and medicinal products that are inhibitors of CYP3A may result in increased plasma concentrations of maribavir (see section 5.2). However, no dose adjustment is needed when maribavir is co-administered with CYP3A inhibitors.

Concomitant administration of strong or moderate CYP3A inducers, (such as rifampicin, rifabutin, carbamazepine, phenobarbital, phenytoin, efavirenz and St John's wort), is expected to significantly

decrease maribavir plasma concentrations, which may result in decrease in efficacy. Therefore, alternative medicinal products with no CYP3A induction potential should be considered. Co-administration of maribavir with strong cytochrome P450 3A (CYP3A) inducers rifampicin, rifabutin or St. John's wort is not recommended.

If co-administration of maribavir with other strong or moderate CYP3A inducers (e.g., carbamazepine, efavirenz, phenobarbital and phenytoin) cannot be avoided, the maribavir dose should be increased to 1 200 mg twice daily (see sections 4.2 and 5.2).

#### Effect of maribavir on other medicinal products

Co-administration of maribavir with valganciclovir and ganciclovir is contraindicated (see section 4.3). LIVTENCITY may antagonise the antiviral effect of ganciclovir and valganciclovir by inhibiting human CMV UL97 serine/threonine kinase, which is required for activation/phosphorylation of ganciclovir and valganciclovir (see sections 4.3 and 5.1).

At therapeutic concentrations, clinically relevant interactions are not expected when maribavir is co-administered with substrates of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2E1, 2D6, and 3A4; UGT1A1, 1A4, 1A6, 1A9, 2B7; bile salt export pump (BSEP); multidrug and toxin extrusion protein (MATE)/2K; organic anion transporters (OAT)1; organic cation transporters (OCT)1 and OCT2; organic anion transporting polypeptide (OATP)1B1 and OATP1B3 based on *in vitro* and clinical interaction results (Table 1 and section 5.2).

Maribavir acted as an inducer of CYP1A2 enzyme *in vitro*. There are no clinical data available to exclude an interaction risk via CYP1A2 induction *in vivo*. Therefore, the concomitant administration of maribavir and medicinal products that are sensitive substrates of CYP1A2 with a narrow therapeutic window (e.g., tizanidine and theophylline) should be avoided due to the risk for lack of efficacy of CYP1A2 substrates.

Co-administration of maribavir increased plasma concentrations of tacrolimus (see Table 1). When the immunosuppressants tacrolimus, cyclosporine, everolimus or sirolimus are co-administered with maribavir, immunosuppressant levels should be frequently monitored throughout treatment with maribavir, especially following initiation and after discontinuation of maribavir and dose adjusted, when needed (see sections 4.4 and Table 1).

Maribavir inhibited P-gp transporter *in vitro* at clinically relevant concentrations. In a clinical study, co-administration of maribavir increased plasma concentrations of digoxin (see Table 1). Therefore, caution should be exercised when maribavir and sensitive P-gp substrates (e.g., digoxin, dabigatran) are co-administered. Serum digoxin concentrations should be monitored, and dose of digoxin may need to be reduced, as needed (see Table 1).

Maribavir inhibited BCRP transporter *in vitro* at clinically relevant concentrations. Therefore, co-administration of maribavir with sensitive BCRP substrates such as rosuvastatin, is expected to increase their exposure and lead to undesirable effects.

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

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

#### General information

If dose adjustments of concomitant medicinal products are made due to treatment with maribavir, doses should be readjusted after treatment with maribavir is completed. Table 1 provides a listing of established or potentially clinically significant medicinal product interactions. The medicinal product

interactions described are based on studies conducted with maribavir or are predicted medicinal product interactions that may occur with maribavir (see sections 4.4 and 5.2).

**Table 1: Interactions and dose recommendations 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
<b>Acid-reducing agents</b>		
antacid (aluminium and magnesium hydroxide oral suspension) (20 mL single dose, maribavir 100 mg single dose)	↔ maribavir AUC 0.89 (0.83, 0.96) C <sub>max</sub> 0.84 (0.75, 0.94)	No dose adjustment is required.
famotidine	Interaction not studied. Expected: ↔ maribavir	No dose adjustment is required.
pantoprazole	Interaction not studied. Expected: ↔ maribavir	No dose adjustment is required.
omeprazole	↔ maribavir ↑ plasma omeprazole/5-hydroxyomeprazole concentration ratio 1.71 (1.51, 1.92) at 2h post-dose (CYP2C19 inhibition)	No dose adjustment is required.
<b>Antiarrhythmics</b>		
digoxin (0.5 mg single dose, 400 mg twice daily maribavir)	↔ digoxin AUC 1.21 (1.10, 1.32) C <sub>max</sub> 1.25 (1.13, 1.38) (P-gp inhibition)	Use caution when maribavir and digoxin are co-administered. Monitor serum digoxin concentrations. The dose of sensitive P-gp substrates such as digoxin may need to be reduced when co-administered with maribavir.
<b>Antibiotics</b>		
clarithromycin	Interaction not studied. Expected: ↑ maribavir (CYP3A inhibition)	No dose adjustment is required.
<b>Anticonvulsants</b>		
carbamazepine phenobarbital phenytoin	Interaction not studied. Expected: ↓ maribavir (CYP3A induction)	A dose adjustment of maribavir to 1 200 mg twice daily is recommended when co-administration with these anticonvulsants.
<b>Antifungals</b>		
ketoconazole (400 mg single dose, maribavir 400 mg single dose)	↑ maribavir AUC 1.53 (1.44, 1.63) C <sub>max</sub> 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) ↔ voriconazole AUC 0.93 (0.83, 1.05)	No dose adjustment is required.

<b>Medicinal product by therapeutic area</b>	<b>Effect on geometric mean ratio (90 % CI) (likely mechanism of action)</b>	<b>Recommendation concerning co-administration with maribavir</b>
	$C_{max}$ 1.00 (0.87, 1.15) (CYP2C19 inhibition)	
<b>Antihypertensives</b>		
diltiazem	Interaction not studied. Expected: ↑ maribavir (CYP3A inhibition)	No dose adjustment is required.
<b>Antimycobacterials</b>		
rifabutin	Interaction not studied. Expected: ↓ maribavir (CYP3A induction)	Co-administration of maribavir and rifabutin is not recommended due to potential for a decrease in efficacy of maribavir.
rifampicin (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 potential for a decrease in efficacy of maribavir.
<b>Antitussives</b>		
dextromethorphan (30 mg single dose, maribavir 400 mg twice daily)	↔ dextrothorphan AUC 0.97 (0.94, 1.00) $C_{max}$ 0.94 (0.88, 1.01) (CYP2D6 inhibition)	No dose adjustment is required.
<b>CNS stimulants</b>		
<b>Herbal products</b>		
St. John's wort ( <i>Hypericum perforatum</i> )	Interaction not studied. Expected: ↓ maribavir (CYP3A induction)	Co-administration of maribavir and St. John's wort is not recommended due to potential for a decrease in efficacy of maribavir.
<b>HIV antiviral agents</b>		
<b>Non-nucleoside reverse transcriptase inhibitors</b>		
Efavirenz Etravirine Nevirapine	Interaction not studied. Expected: ↓ maribavir (CYP3A induction)	A dose adjustment of maribavir to 1 200 mg twice daily is recommended when co-administration with these a non-nucleoside reverse transcriptase inhibitors.
<b>Nucleoside reverse transcriptase inhibitors</b>		
Tenofovir disoproxil Tenofovir alafenamide Abacavir Lamivudine Emtricitabine	Interaction not studied. Expected: ↔ maribavir ↔ nucleoside reverse transcriptase inhibitors	No dose adjustment is required.
<b>Protease inhibitors</b>		

<b>Medicinal product by therapeutic area</b>	<b>Effect on geometric mean ratio (90 % CI) (likely mechanism of action)</b>	<b>Recommendation concerning co-administration with maribavir</b>
ritonavir- boosted protease inhibitors (atazanavir, darunavir, lopinavir)	Interaction not studied. Expected: ↑ maribavir (CYP3A inhibition)	No dose adjustment is required.
<b>Integrase strand transfer inhibitors</b>		
dolutegravir	Interaction not studied. Expected: ↔ maribavir ↔ dolutegravir	No dose adjustment is required.
<b>HMG-CoA reductase inhibitors</b>		
atorvastatin fluvastatin simvastatin	Interaction not studied. Expected: ↑ HMG-CoA reductase inhibitors (BCRP inhibition)	No dose adjustment is required.
rosuvastatin <sup>a</sup>	Interaction not studied. Expected: ↑ rosuvastatin (BCRP inhibition)	The patient should be closely monitored for rosuvastatin-related events, especially the occurrence of myopathy and rhabdomyolysis.
<b>Immunosuppressants</b>		
cyclosporine <sup>a</sup> everolimus <sup>a</sup> sirolimus <sup>a</sup>	Interaction not studied. Expected: ↑ cyclosporine, everolimus, sirolimus (CYP3A/P-gp inhibition)	Frequently monitor cyclosporine, everolimus and sirolimus levels, especially following initiation and after discontinuation of maribavir and adjust dose, as needed.
tacrolimus <sup>a</sup>	↑ tacrolimus AUC 1.51 (1.39, 1.65) C <sub>max</sub> 1.38 (1.20, 1.57) C <sub>trough</sub> 1.57 (1.41, 1.74) (CYP3A/P-gp inhibition)	Frequently monitor tacrolimus levels, especially following initiation and after discontinuation of maribavir and adjust dose, as needed.
<b>Oral anticoagulants</b>		
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.
<b>Oral contraceptives</b>		
systemically acting oral contraceptive steroids	Interaction not studied. Expected: ↔ oral contraceptive steroids (CYP3A inhibition)	No dose adjustment is required.
<b>Sedatives</b>		
midazolam (0.075 mg/kg single dose, maribavir 400 mg twice daily for 7 days)	↔ midazolam  AUC 0.89 (0.79, 1.00) C <sub>max</sub> 0.82 (0.70, 0.96)	No dose adjustment is required.

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

CI = Confidence Interval

\*AUC<sub>0-∞</sub> for single dose, AUC<sub>0-12</sub> for twice daily dose daily.

Note: the table is not extensive but provides examples of clinically relevant interactions.

<sup>a</sup> Refer to the respective prescribing information.

## Paediatric population

Interaction studies have only been performed in adults.

## **4.6 Fertility, pregnancy and lactation**

### Pregnancy

There are no data of maribavir use in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). LIVTENCITY is not recommended during pregnancy and in women of childbearing potential not using contraception.

Maribavir is not expected to affect the plasma concentrations of systemically acting oral contraceptive steroids (see Section 4.5).

### Breast-feeding

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

### Fertility

Fertility studies were not conducted in humans with LIVTENCITY. No effects on fertility or reproductive performance were noted in rats in a combined fertility and embryofetal development study, however, a decrease in sperm straight line velocity was observed at doses  $\geq 100$  mg/kg/day (which is estimated to be  $< 1$  times the human exposure at the recommended human dose [RHD]). There were no effects on reproductive organs in either males or females in nonclinical studies in rats and monkeys (see section 5.3).

## **4.7 Effects on ability to drive and use machines**

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

## **4.8 Undesirable effects**

### Summary of the safety profile

Adverse events were collected during the treatment phase and follow-up phase through Study Week 20 in the Phase 3 study (see section 5.1). The mean exposures (SD) for LIVTENCITY was 48.6 (13.82) days with 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 level increased, and vomiting (all occurring at  $< 1\%$ ).

### Tabulated list of adverse reactions

The adverse reactions are listed below by body system organ class and frequency. Frequencies are defined as follows: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1\ 000$  to  $< 1/100$ ), rare ( $\geq 1/10\ 000$  to  $< 1/1\ 000$ ) or very rare ( $< 1/10\ 000$ ).

**Table 2: Adverse reactions identified with LIVTENCITY**

<b>System Organ Class</b>	<b>Frequency</b>	<b>Adverse reactions</b>
<b>Nervous system disorders</b>	Very common	Taste disturbance*

	Common	Headache
<b>Gastrointestinal disorders</b>	Very Common	Diarrhoea, Nausea, Vomiting
	Common	Abdominal pain upper
<b>General disorders and administration site conditions</b>	Very common	Fatigue
	Common	Decreased appetite
<b>Investigations</b>	Common	Immunosuppressant drug level increased*, Weight decreased

#### 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.

##### *Increases in plasma levels of immunosuppressants*

Immunosuppressant drug level increase (comprised of the preferred terms immunosuppressant drug level increased and drug level increased) occurred in 9% of patients treated with LIVTENCITY. LIVTENCITY has the potential to increase the drug concentrations of immunosuppressants that are CYP3A and/or P-gp substrates with narrow therapeutic ranges (including tacrolimus, cyclosporine, sirolimus and everolimus). (See sections 4.4, 4.5 and 5.2).

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## **4.9 Overdose**

In Study 303, an accidental overdose of a single extra dose occurred in 1 LIVTENCITY-treated subject on Day 13 (1 200 mg total daily dose). No adverse reactions were reported.

In Study 202, 40 subjects were exposed to doses of 800 mg twice daily and 40 subjects were exposed to 1 200 mg twice daily for a mean of approximately 90 days. In Study 203, 40 subjects were exposed to doses of 800 mg twice daily and 39 subjects were exposed to 1 200 mg twice daily for a maximum of 177 days. There were no appreciable differences in the safety profile in either study compared to the 400 mg twice daily group in Study 303 in which subjects received maribavir for a maximum of 60 days.

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, direct acting antivirals, ATC code: J05AX10.

#### Mechanism of action

Maribavir is a competitive inhibitor of the UL97 protein kinase. UL97 inhibition occurs at the viral DNA replication phase, inhibiting UL97 serine/threonine kinase by competitively inhibiting the binding of ATP to the kinase ATP-binding site, without affecting the concatemer maturation process, abolishing phosphotransferase inhibiting CMV DNA replication and maturation, CMV DNA encapsidation, and CMV DNA nuclear egress.

#### Antiviral activity

Maribavir inhibited human CMV replication in virus yield reduction, DNA hybridization, and plaque reduction assays in human lung fibroblast cell line (MRC-5), human embryonic kidney (HEK), and human foreskin fibroblast (MRHF) cells. The EC<sub>50</sub> 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<sub>50</sub> values were 0.1 µM (n=10, range 0.03-0.13 µM) and 0.28 µM (n=10, range 0.12-0.56 µM) using DNA hybridization and plaque reduction assays, respectively. No significant difference in EC<sub>50</sub> values across the four human CMV glycoprotein B genotypes (N = 2, 1, 4, and 1 for gB1, gB2, gB3, and gB4, respectively) was seen.

#### Combination antiviral activity

When maribavir was tested in *in vitro* combination with other antiviral compounds, strong antagonism was seen with ganciclovir.

No antagonism was seen in combination with cidofovir, foscarnet and letermovir.

#### Viral resistance

##### *In cell culture*

Maribavir does not affect the UL54 encoded DNA polymerase that, when presenting certain mutations, confers resistance to ganciclovir/valganciclovir, foscarnet and/or cidofovir. Mutations conferring resistance to maribavir have been identified on gene UL97: L337M, F342Y, V353A, V356G, L397R, T409M, H411L/N/Y, D456N, V466G C480F, P521L, and Y617del. These mutations confer resistance that ranges from 3.5-fold to > 200-fold increase in EC<sub>50</sub> values. UL27 gene variants (R233S, W362R, W153R, L193F, A269T, V353E, L426F, E22stop, W362stop, 218delC, and 301311del) conferred only mild maribavir resistance (< 5fold increase in EC<sub>50</sub>), while L335P conferred high maribavir resistance.

##### *In clinical studies*

In Phase 2 Study 202 and Study 203 evaluating maribavir in 279 HSCT or SOT 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 mutations 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<sub>50</sub> compared with the wild-type strain, whereas the pUL27 mutation G344D showed no difference in maribavir EC<sub>50</sub> as compared to the wild-type strain.

In Phase 3 Study 303 evaluating maribavir in patients with phenotypic resistance to valganciclovir/ganciclovir, DNA sequence analysis of the entire coding regions of pUL97 and pUL27 was performed on 134 paired sequences from maribavir-treated patients. The treatment-emergent pUL97 substitutions F342Y (4.5-fold), T409M (78-fold), H411L/N/Y (69-, 9-, and 12-fold, respectively), and/or C480F (224-fold) were detected in 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 culture 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 substitutions (RAS) to Investigator assigned treatment (IAT). Of these 24 had treatment-emergent C480F or the F342Y RAS, both are cross-resistant to both ganciclovir/valganciclovir and maribavir. Of these 24 patients, 1 (4%) 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 > 4.5-fold. Other vGCV/GCV resistance pathways have not been evaluated for cross-resistance to maribavir. pUL54 DNA polymerase substitutions conferring resistance to vGCV/GCV, cidofovir, or foscarnet remained susceptible to maribavir.

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

### Clinical efficacy

A Phase 3, multi-centre, randomised, open-label, active-controlled superiority study (Study SHP620-303) assessed the efficacy and safety of LIVTENCITY treatment compared to Investigator assigned treatment (IAT) in 352 HSCT and SOT recipients with CMV infections that were refractory to treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir, including CMV infections with or without confirmed resistance to 1 or more anti-CMV agents. Refractory CMV infection was defined as documented failure to achieve > 1 log<sub>10</sub> decrease in CMV DNA level in whole blood or plasma after a 14-day or longer treatment period with intravenous ganciclovir/oral valganciclovir, intravenous foscarnet, or intravenous cidofovir. This definition was applied to the current CMV infection and the most recently administered anti-CMV agent.

Patients were stratified by transplant type (HSCT or SOT) and screening CMV DNA levels and then randomised in a 2:1 ratio to receive LIVTENCITY 400 mg twice daily or IAT (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 3 below.

**Table 3: Summary of the baseline disease characteristics of the study population in Study 303.**

<b>Characteristic<sup>a</sup></b>	<b>IAT (N=117)</b>	<b>LIVTENCITY 400 mg Twice Daily (N=235)</b>
<b>IAT treatment prior to randomization, n (%)<sup>b</sup></b>		
Ganciclovir/ Valganciclovir	98 (84)	204 (87)
Foscarnet	18 (15)	27 (12)
Cidofovir	1 (1)	4 (2)
<b>IAT treatment after randomization, n (%)</b>		
Foscarnet	47 (41)	n/a
Ganciclovir/ Valganciclovir	56 (48)	n/a
Cidofovir	6 (5)	n/a
Foscarnet+ Ganciclovir/Valganciclovir	7 (6)	n/a
<b>Transplant type, n (%)</b>		
HSCT	48 (41)	93 (40)
SOT <sup>c</sup>	69 (59)	142 (60)
Kidney <sup>d</sup>	32 (46)	74 (52)
Lung <sup>d</sup>	22 (32)	40 (28)
Heart <sup>d</sup>	9 (13)	14 (10)
Multiple <sup>d</sup>	5 (7)	5 (4)
Liver <sup>d</sup>	1 (1)	6 (4)
Pancreas <sup>d</sup>	0	2 (1)
Intestine <sup>d</sup>	0	1 (1)
<b>CMV DNA levels category as reported by central laboratory, n (%)<sup>e</sup></b>		
High	7 (6)	14 (6)
Intermediate	25 (21)	68 (29)
Low	85 (73)	153 (65)
<b>Baseline symptomatic CMV infection<sup>f</sup></b>		
No	109 (93)	214 (91)
Yes <sup>f</sup>	8 (7)	21 (9)
CMV syndrome (SOT only), n (%) <sup>d,f,g</sup>	7 (88)	10 (48)
Tissue invasive disease, n (%) <sup>f, d, g</sup>	1 (13)	12 (57)

CMV=cytomegalovirus, DNA=deoxyribonucleic acid, HSCT=haematopoietic stem cell transplant, IAT=investigator assigned anti-CMV treatment, max=maximum, min=minimum, N=number of patients, SOT=solid organ transplant.

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

<sup>b</sup> Percentages are based on the number of subjects in the Randomized set within each column. Most recent anti-CMV agent, used to confirm refractory eligibility criteria.

<sup>c</sup> The most recent transplant.

<sup>d</sup> Percentages are based on the number of patients within the category.

<sup>e</sup> Viral load was defined for analysis by the baseline central specialty laboratory plasma CMV DNA qPCR results as high ( $\geq 91,000$  IU/mL), intermediate ( $\geq 9,100$  and  $< 91,000$  IU/mL), and low ( $< 9,100$  IU/mL).

<sup>f</sup> Confirmed by Endpoint Adjudication Committee (EAC).

<sup>g</sup> 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 ( $< \text{LLOQ}$ ; i.e.,  $< 137$  IU/mL) at Week 8 regardless of whether either study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy. 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. 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.

For the primary endpoint, LIVTENCITY was superior to IAT (56% vs. 24%, respectively,  $p < 0.001$ ). For the key secondary endpoint, 19% vs. 10% achieved both CMV viraemia clearance and CMV infection symptom control in the LIVTENCITY and IAT group, respectively ( $p=0.013$ ) (See Table 4).

**Table 4: Primary and key secondary efficacy endpoint analysis (randomised set) in Study 303**

	<b>IAT (N=117) n (%)</b>	<b>LIVTENCITY 400 mg twice daily (N=235) n (%)</b>
<b>Primary endpoint: CMV viraemia clearance response at week 8</b>		
Overall		
Responders	28 (24)	131 (56)
Adjusted difference in proportion of responders (95% CI) <sup>a</sup>		32.8 (22.8, 42.7)
p-value: adjusted <sup>a</sup>		< 0.001
<b>Key secondary endpoint: Achievement of CMV viraemia clearance and CMV infection symptom control<sup>b</sup> at week 8, with maintenance through week 16<sup>b</sup></b>		
Overall		
Responders	12 (10)	44 (19)
Adjusted difference in proportion of responders (95% CI) <sup>a</sup>		9.45 (2.0, 16.9)
p-value: Adjusted <sup>a</sup>		0.013

CI=confidence interval; CMV=cytomegalovirus; HSCT=haematopoietic stem cell transplant; IAT=investigator-assigned anti-CMV treatment; N=number of patients; SOT=solid organ transplant.

<sup>a</sup> Cochran-Mantel-Haenszel weighted average approach was used for the adjusted difference in proportion (maribavir-IAT), the corresponding 95% CI, and the p-value after adjusting for the transplant type and baseline plasma CMV DNA concentration.

<sup>b</sup> 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 treatment effect was consistent across transplant type, age group, and the presence of CMV syndrome/disease at baseline. However, LIVTENCITY was less effective against subjects with increased CMV DNA levels ( $\geq 50\,000$  IU/mL) and patients with absence of genotypic resistance (see table 5).

**Table 5: Percentage of Responders by subgroup in Study 303**

	IAT (N=117)		LIVTENCITY 400 mg Twice Daily (N=235)	
	n/N	%	n/N	%
<b>Transplant type</b>				
SOT	18/69	26	79/142	56
HSCT	10/48	21	52/93	56
<b>Baseline CMV DNA viral load</b>				
Low	21/85	25	95/153	62
Intermediate/High	7/32	22	36/82	44
<b>Genotypic resistance to other anti-CMV agents</b>				
Yes	14/69	20	76/121	63
No	11/34	32	42/96	44
<b>CMV syndrome/disease at baseline</b>				
Yes	1/8	13	10/21	48
No	27/109	25	121/214	57
<b>Age Group</b>				
18 to 44 years	8/32	25	28/55	51
45 to 64 years	19/69	28	71/126	56
$\geq 65$ years	1/16	6	32/54	59

CMV=cytomegalovirus, DNA=deoxyribonucleic acid, HSCT=haematopoietic stem cell transplant, SOT=solid organ transplant

### Recurrence

The secondary endpoint of recurrence of CMV viraemia was reported in 57% of the maribavir treated patients and in 34% of the IAT treated patients. Of these, 18% in the maribavir group had recurrence of CMV viraemia while on-treatment compared to 12% the IAT group. Recurrence of CMV viraemia during follow up was seen in 39% of patients in the maribavir group and in 22% of the patients in the IAT group.

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

### Paediatric population

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 4.2).

## **5.2 Pharmacokinetic properties**

Maribavir pharmacological activity is due to the parent medicinal product. The pharmacokinetics of maribavir have been characterised following oral administration in healthy subjects and transplant patients. Maribavir exposure increased in an approximately dose proportionally manner. In healthy subjects, the geometric mean steady-state AUC<sub>0-t</sub>, C<sub>max</sub> and C<sub>trough</sub> values were 101  $\mu\text{g}\cdot\text{h}/\text{mL}$ , 16.4  $\mu\text{g}/\text{mL}$  and 2.89  $\mu\text{g}/\text{mL}$ , respectively, following 400 mg twice daily oral maribavir doses.

In transplant recipients, maribavir steady state exposure following oral administration of 400 mg twice daily doses are provided below, based on a population pharmacokinetics analysis. Steady-state was

reached in 2 days, with an accumulation ratio of 1.47 for AUC and 1.37 for C<sub>max</sub>. The intrasubject variability (< 22%) and intersubject variability (< 37%) in maribavir PK parameters are low to moderate.

**Table 6: Maribavir pharmacokinetic properties in transplant recipients based on a population pharmacokinetics analysis**

Parameter GM (% CV)	AUC <sub>0-<math>\tau</math></sub> $\mu\text{g}^*\text{h/mL}$	C <sub>max</sub> $\mu\text{g/mL}$	C <sub>trough</sub> $\mu\text{g/mL}$
Maribavir 400 mg twice daily	142 (48.5%)	20.1 (35.5%)	5.43 (85.9%)
GM: Geometric mean, % CV: Geometric coefficient of variation			

### Absorption

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 crushed tablet through nasogastric (NG)/orogastric tubes or co-administration with proton pump inhibitors (PPIs), histamine H<sub>2</sub> receptor antagonists (H<sub>2</sub> blockers) or antacids.

### *Effect of food*

In healthy subjects, oral administration of a single 400 mg dose of maribavir with a high fat, high caloric meal resulted in no change in the overall exposure (AUC) and a 28% decrease in C<sub>max</sub> of maribavir, which was not considered clinically relevant.

### Distribution

Based on population pharmacokinetic analyses, the apparent steady-state volume of distribution is estimated to be 24.9 L.

*In vitro* binding of maribavir to human plasma proteins was 98.0% over the concentration range of 0.05-200  $\mu\text{g/mL}$ . *Ex vivo* protein binding of maribavir (98.5%-99.0%) was consistent with *in vitro* data, with no apparent difference observed among healthy subjects, subjects with hepatic (moderate) or renal (mild, moderate or severe) impairment, human immunodeficiency virus (HIV) patients, or transplant patients.

Maribavir may cross the blood-brain barrier in humans but CNS penetration is expected to be low compared to plasma levels (see section 4.4 and 5.3).

*In vitro* data indicate that maribavir is a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and organic cation transporter 1 (OCT1) transporters. Changes in maribavir plasma concentrations due to inhibition of P-gp/BCRP/OCT1 were not clinically relevant.

### Biotransformation

Maribavir is primarily eliminated by hepatic metabolism via CYP3A4 (primary metabolic pathway fraction metabolised estimated to be at least 35%), with secondary contribution from CYP1A2 (fraction metabolised estimated at no more than 25%). The major metabolite of maribavir is formed by N-dealkylation of the isopropyl moiety and is considered pharmacologically inactive. The metabolic ratio for this major metabolite in plasma was 0.15-0.20. 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.

Based on *in vitro* studies, metabolism of maribavir is not mediated by CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A5, 1A4, UGT1A6, UGT1A10, or UGT2B15.

### Elimination

The elimination half-life and oral clearance of maribavir are estimated at 4.3 hours and 2.67 L/h, respectively, in transplant patients. After single dose oral administration of [<sup>14</sup>C]-maribavir, approximately 61% and 14% of the radioactivity were recovered in urine and faeces, respectively, primarily as the major and inactive metabolite. Urinary excretion of unchanged maribavir is minimal.

### Special populations

#### *Renal impairment*

No clinically significant effect of mild, moderate or severe renal impairment (measured creatinine clearance ranging from 12 to 70 mL/min) was observed on maribavir total PK parameters following a single dose of 400 mg maribavir. The difference in maribavir PK parameters between subjects with mild/moderate or severe renal impairment and subjects with normal renal function was < 9%. As maribavir is highly bound to plasma proteins, it is unlikely that maribavir will be significantly removed by haemodialysis or peritoneal dialysis.

#### *Hepatic impairment*

No clinically significant effect of moderate hepatic impairment (Child-Pugh Class B, score of 7-9) was observed on total or unbound maribavir PK parameters following a single dose of 200 mg of maribavir. Compared to the healthy control subjects, AUC and C<sub>max</sub> were 26% and 35% higher, respectively, in subjects with moderate hepatic impairment. It is not known whether the exposure to maribavir will increase in patients with severe 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 clinically significant effect on the pharmacokinetics of maribavir based on population PK analysis.

#### *Transplant types*

Transplant types (HSCT vs. SOT) or between SOT types (liver, lung, kidney, or heart) or presence of gastrointestinal (GI) graft-versus host disease (GvHD) do not have a clinically significant impact on PK of maribavir.

## **5.3 Preclinical safety data**

### General

Regenerative anaemia and mucosal cell hyperplasia in the intestinal tract, observed with dehydration was noted in rats and monkeys, together with clinical observations of soft to liquid stool, and electrolyte changes (in monkeys only). A no observed adverse effect level (NOAEL) was not established in monkeys and was < 100 mg/kg/day, which is approximately 0.25 the human exposure at the recommended human dose (RHD). In rats the NOAEL was 25 mg/kg/day, at which exposures were 0.05 and 0.1 times the human exposure at the RHD in males and females, respectively.

Maribavir did not demonstrate phototoxicity *in vitro*, therefore, the potential for phototoxicity in humans is considered unlikely.

Maribavir was detected at low levels in the choroid plexus of rats and the brain and CSF of the monkey (see section 4.4 and 5.2).

## Carcinogenesis

No carcinogenic potential was identified in rats up to 100 mg/kg/day at which exposures in males and females were 0.2 and 0.36 times, respectively the human exposure at the RHD. In male mice, an equivocal elevation in the incidence of haemangioma, haemangiosarcoma, and combined haemangioma/ haemangiosarcoma across multiple tissues at 150 mg/kg/day is of uncertain relevance in terms of its translation to human risk given the lack of an effect in female mice or in rats after 104 weeks of administration, lack of neoplastic proliferative effects in male and female mice after 13 weeks administration, the negative genotoxicity package and the difference in duration of administration in humans. There were no carcinogenic findings at the next lower dose of 75 mg/kg/day, which is approximately 0.35 and 0.25 in males and females, respectively, the human exposure at the RHD.

## Mutagenesis

Maribavir was not mutagenic in a bacterial mutation assay, nor 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.

## Reproduction

### *Fertility*

In the combined fertility and embryofoetal development study in rats, there were no effects of maribavir on fertility. However, in male rats decreases in sperm straight line velocity, were observed at doses  $\geq 100$  mg/kg/day (which is estimated to be less than the human exposure at the RHD), but without any impact on male fertility.

### Prenatal and postnatal development

In a combined fertility and embryofoetal development study in rats, maribavir was not teratogenic and had no effect on embryofoetal growth or development at doses up to 400 mg/kg/day. A decrease in the number of viable foetuses due to increase in early resorptions and post-implantation losses was observed in females at all tested maribavir doses which were also maternally toxic. The lowest dose corresponded to approximately half the human exposure at the RHD. In the pre and postnatal developmental toxicity study conducted in rats, decreased pup survival due to poor maternal care and reduced body weight gain associated with a delay in developmental milestones (pinna detachment, eye opening and preputial separation) were observed at maribavir doses  $\geq 150$  mg/kg/day. Postnatal development was not affected at 50 mg/kg/day. Fertility and mating performance of the F<sub>1</sub> generation, and their ability to maintain pregnancy and to deliver live offspring, was unaffected up to 400 mg/kg/day.

In rabbits, maribavir was not teratogenic at doses up to 100 mg/kg/day (approximately 0.45 times the human exposure at the RHD).

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Tablet core

Microcrystalline cellulose (E460(i))  
Sodium starch glycolate  
Magnesium stearate (E470b)

## Film-coating

Polyvinyl alcohol (E1203)  
Macrogol (polyethylene glycol) (E1521)  
Titanium dioxide (E171)  
Talc (E553b)  
Brilliant blue FCF aluminum lake (EU) (E133)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

36 months.

### **6.4 Special precautions for storage**

Do not store above 30 °C.

### **6.5 Nature and contents of container**

High-density polyethylene (HDPE) bottles with child resistant cap.

Pack-sizes of 28, 56 or 112 (2 bottles of 56) film-coated tablets.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

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

## **7. MARKETING AUTHORISATION HOLDER**

Takeda Pharmaceuticals International AG Ireland Branch  
Block 2 Miesian Plaza  
50-58 Baggot Street Lower  
Dublin 2  
D02 HW68  
Ireland  
E-mail: medinfoEMEA@takeda.com

## **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/22/1672/001  
EU/1/22/1672/002  
EU/1/22/1672/003

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 09 November 2022

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **ANNEX II**

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## **A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer(s) responsible for batch release

Takeda Ireland Limited  
Bray Business Park  
Kilruddery  
Co. Wicklow  
Ireland

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## **C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

## **D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

LIVTENCITY 200 mg film-coated tablets  
maribavir

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 200 mg of maribavir.

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

28 film-coated tablets

56 film-coated tablets

112 film-coated tablets (2 bottles of 56)

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30 °C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Takeda Pharmaceuticals International AG Ireland Branch  
Block 2 Miesian Plaza  
50-58 Baggot Street Lower  
Dublin 2  
D02 HW68  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/22/1672/001 28 film-coated tablets  
EU/1/22/1672/002 56 film-coated tablets  
EU/1/22/1672/003 112 film-coated tablets (2 bottles of 56)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

LIVTENCITY 200 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**BOTTLE LABEL**

**1. NAME OF THE MEDICINAL PRODUCT**

LIVTENCITY 200 mg film-coated tablets  
maribavir

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 200 mg of maribavir.

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet

28 film-coated tablets

56 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30 °C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Takeda Pharmaceuticals International AG Ireland Branch  
Dublin 2  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/22/1672/001 28 film-coated tablets  
EU/1/22/1672/002 56 film-coated tablets  
EU/1/22/1672/003 112 film-coated tablets (2 bottles of 56)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

**17. UNIQUE IDENTIFIER – 2D BARCODE**

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

**B. PACKAGE LEAFLET**

## Package leaflet: Information for the patient

### LIVTENCITY 200 mg film-coated tablets maribavir

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

#### **Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What LIVTENCITY is and what it is used for
2. What you need to know before you take LIVTENCITY
3. How to take LIVTENCITY
4. Possible side effects
5. How to store LIVTENCITY
6. Contents of the pack and other information

#### **1. What LIVTENCITY is and what it is used for**

LIVTENCITY is an antiviral medicine that contains the active substance maribavir.

It is a medicine used to treat adults who have had an organ or bone marrow transplant and developed a CMV ('cytomegalovirus') infection that did not go away or came back again after taking another antiviral medicine.

CMV is a virus that a lot of people have without symptoms and normally just stays in the body without causing any harm. However, if your immune system is weakened after you get an organ or bone marrow transplant, you may be at higher risk of becoming ill from CMV.

#### **2. What you need to know before you take LIVTENCITY**

##### **Do not take LIVTENCITY**

- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6).
- if you take either of these medicines:
  - ganciclovir (used to manage CMV infection)
  - valganciclovir (used to manage CMV infection)

You should not be given LIVTENCITY if any of the above apply to you. If you are not sure, talk to your doctor, pharmacist or nurse before you are given LIVTENCITY.

##### **Warnings and precautions**

Talk to your doctor or pharmacist before taking LIVTENCITY if you are already being treated with cyclosporine, tacrolimus, sirolimus or everolimus (medicines to prevent transplant rejection).

Additional blood tests may be needed to check the blood levels of these medicines. High levels of these medicines may cause serious side effects.

### **Children and adolescents**

LIVTENCITY is not for use in children and adolescents under 18 years old. This is because LIVTENCITY has not been tested in this age group.

### **Other medicines and LIVTENCITY**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because LIVTENCITY may affect the way other medicines work, and other medicines may affect how LIVTENCITY works. Your doctor or pharmacist will tell you if it is safe to take LIVTENCITY with other medicines.

There are some medicines you must not take with LIVTENCITY. See list under “Do not take LIVTENCITY”.

Also tell your doctor if you are taking any of the following medicines. This is because your doctor may have to change your medicines or change the dose of your medicines:

- rifabutin, rifampicin – for tuberculosis (TB) or related infections
- St. John's wort (*Hypericum perforatum*) – a herbal medicine for depression and sleep problems
- statins, such as atorvastatin, fluvastatin, rosuvastatin, simvastatin, pravastatin, pitavastatin – for high cholesterol
- carbamazepine, phenobarbital, phenytoin – usually for fits or seizures (epilepsy)
- efavirenz, etravirine, nevirapine - used to treat HIV infection
- antacid (aluminium and magnesium hydroxide oral suspension) – for heartburn or indigestion due to excess stomach acid
- famotidine – for heartburn or indigestion due to excess stomach acid
- digoxin – heart medicine
- clarithromycin– antibiotic
- ketoconazole and voriconazole – for fungal infections
- diltiazem – heart medicine
- dextromethorphan – cough medicine
- warfarin – anticoagulant
- oral contraceptive steroids – for birth control
- midazolam – used as a sedative

You can ask your doctor, pharmacist or nurse for a list of medicines that may interact with LIVTENCITY.

### **Pregnancy**

If you are pregnant, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before taking this medicine. LIVTENCITY is not recommended in pregnancy. This is because it has not been studied in pregnancy and it is not known if LIVTENCITY will harm your baby while you are pregnant.

### **Breast-feeding**

If you are breast-feeding or are planning to breast-feed, tell your doctor before taking this medicine. Breast-feeding is not recommended while taking LIVTENCITY. This is because it is not known if LIVTENCITY can pass into your breast milk or if this would affect your baby.

### **Driving and using machines**

LIVTENCITY has no influence on your ability to drive or to use machines.

### **LIVTENCITY contains sodium**

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

### **3. How to take LIVTENCITY**

Always take this medicine exactly as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

The recommended dose is 400 mg twice a day. That means you take two tablets of LIVTENCITY 200 mg in the morning, and another two tablets of 200 mg in the evening. You can take this medicine with or without food, as a whole tablet or a crushed tablet.

#### **If you take more LIVTENCITY than you should**

If you take too much LIVTENCITY, tell your doctor straight away.

#### **If you forget to take LIVTENCITY**

If you miss a dose, and there are less than 3 hours left until your next regular dose is due, then skip the missed dose and go back to your regular schedule. Do not take a double dose to make up for a forgotten dose.

#### **If you stop taking LIVTENCITY**

Even if you feel better, do not stop taking LIVTENCITY without talking to your doctor. Taking LIVTENCITY as recommended should give you the best chance of clearing CMV infection and/or disease.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

### **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them. Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

**Very common** (may affect more than 1 in 10 people):

- changes in the way things taste
- feeling sick (nausea)
- diarrhoea
- being sick (vomiting)
- tiredness (fatigue)

**Common** (may affect up to 1 in 10 people):

- Increased blood levels of medicines used to prevent transplant rejections
- stomach (abdominal) pain
- loss of appetite
- headache
- weight loss

#### **Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system listed in Appendix V**. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store LIVTENCITY

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date that is stated on the carton and bottle label after EXP. The expiry date refers to the last day of that month.

Do not store above 30 °C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

## 6. Contents of the pack and other information

### What LIVTENCITY contains

- The active substance is maribavir. Each film-coated tablet contains 200 mg maribavir
- The other ingredients (excipients) are
  - Tablet core:
  - Microcrystalline cellulose (E460(i)), Sodium starch glycolate (see section 2), Magnesium stearate (E470b)
  - Film coating:
  - Polyvinyl alcohol (E1203), Macrogol (i.e. polyethylene glycol) (E1521), Titanium dioxide (E171), Talc (E553b), Brilliant blue FCF aluminum lake (EU) (E133)

### What LIVTENCITY looks like and contents of the pack

LIVTENCITY 200 mg film coated tablets are blue, oval shaped convex debossed with “SHP” on one side and “620” on the other side.

The tablets are packaged in high-density polyethylene (HDPE) bottles with child resistant cap contains either 28, 56 or 112 (2 bottles of 56) film-coated tablets.

Not all pack sizes may be marketed.

### Marketing Authorisation Holder

Takeda Pharmaceuticals International AG Ireland Branch  
Block 2 Miesian Plaza  
50-58 Baggot Street Lower  
Dublin 2  
D02 HW68  
Ireland

### Manufacturer

Takeda Ireland Limited  
Bray Business Park  
Kilruddery  
Co. Wicklow  
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**  
Takeda Belgium NV  
Tél/Tel: +32 2 464 06 11  
medinfoEMEA@takeda.com

**България**  
Такеда България ЕООД  
Тел.: +359 2 958 27 36  
medinfoEMEA@takeda.com

**Česká republika**  
Takeda Pharmaceuticals Czech Republic s.r.o.  
Tel: + 420 234 722 722  
medinfoEMEA@takeda.com

**Danmark**  
Takeda Pharma A/S  
Tlf: +45 46 77 10 10  
medinfoEMEA@takeda.com

**Deutschland**  
Takeda GmbH  
Tel: +49 (0)800 825 3325  
medinfoEMEA@takeda.com

**Eesti**  
Takeda Pharma AS  
Tel: +372 6177 669  
medinfoEMEA@takeda.com

**Ελλάδα**  
Takeda ΕΛΛΑΣ Α.Ε.  
Τηλ: +30 210 6387800  
medinfoEMEA@takeda.com

**España**  
Takeda Farmacéutica España S.A.  
Tel: +34 917 90 42 22  
medinfoEMEA@takeda.com

**France**  
Takeda France SAS  
Tél: + 33 1 40 67 33 00  
medinfoEMEA@takeda.com

**Hrvatska**  
Takeda Pharmaceuticals Croatia d.o.o.  
Tel: +385 1 377 88 96  
medinfoEMEA@takeda.com

**Ireland**  
Takeda Products Ireland Ltd  
Tel: 1800 937 970  
medinfoEMEA@takeda.com

**Lietuva**  
Takeda, UAB  
Tel: +370 521 09 070  
medinfoEMEA@takeda.com

**Luxembourg/Luxemburg**  
Takeda Belgium NV  
Tél/Tel: +32 2 464 06 11  
medinfoEMEA@takeda.com

**Magyarország**  
Takeda Pharma Kft.  
Tel.: +36 1 270 7030  
medinfoEMEA@takeda.com

**Malta**  
Takeda HELLAS S.A.  
Tel: +30 210 6387800  
medinfoEMEA@takeda.com

**Nederland**  
Takeda Nederland B.V.  
Tel: +31 20 203 5492  
medinfoEMEA@takeda.com

**Norge**  
Takeda AS  
Tlf: +47 800 800 30  
medinfoEMEA@takeda.com

**Österreich**  
Takeda Pharma Ges.m.b.H.  
Tel: +43 (0) 800-20 80 50  
medinfoEMEA@takeda.com

**Polska**  
Takeda Pharma Sp. z o.o.  
Tel.: +48223062447  
medinfoEMEA@takeda.com

**Portugal**  
Takeda Farmacêuticos Portugal, Lda.  
Tel: + 351 21 120 1457  
medinfoEMEA@takeda.com

**România**  
Takeda Pharmaceuticals SRL  
Tel: +40 21 335 03 91  
medinfoEMEA@takeda.com

**Slovenija**  
Takeda Pharmaceuticals farmacevtska družba d.o.o.  
Tel: + 386 (0) 59 082 480  
medinfoEMEA@takeda.com

**Ísland**

Vistor hf.  
Sími: +354 535 7000  
medinfoEMEA@takeda.com

**Italia**

Takeda Italia S.p.A.  
Tel: +39 06 502601  
medinfoEMEA@takeda.com

**Κύπρος**

Takeda Ελλάς Α.Ε.  
Τηλ.: +30 210 6387800  
medinfoEMEA@takeda.com

**Latvija**

Takeda Latvia SIA  
Tel: +371 67840082  
medinfoEMEA@takeda.com

**Slovenská republika**

Takeda Pharmaceuticals Slovakia s.r.o.  
Tel: +421 (2) 20 602 600  
medinfoEMEA@takeda.com

**Suomi/Finland**

Takeda Oy  
Puh/Tel: 0800 774 051  
medinfoEMEA@takeda.com

**Sverige**

Takeda Pharma AB  
Tel: 020 795 079  
medinfoEMEA@takeda.com

**United Kingdom (Northern Ireland)**

Takeda UK Ltd  
Tel: +44 (0) 2830 640 902  
medinfoEMEA@takeda.com

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**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>.