

▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

LIVTENCITY® (maribavir) Tablets

1 NAME OF THE MEDICINE

Maribavir

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

LIVTENCITY is available in 200 mg immediate-release tablets and is intended for oral administration. Each film-coated tablet contains 200 mg of maribavir, a potent, selective, antiviral drug belonging to the benzimidazole ribosides class.

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Film-coated tablets.

Appearance

Blue, film-coated, oval-shaped, convex tablet that is de-bossed with 'SHP' on one side and '620' on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of adults with post-transplant cytomegalovirus (CMV) infection and disease resistant, refractory or intolerant to one or more prior therapies (see 4.3 CONTRAINDICATIONS and, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.2 DOSE AND METHOD OF ADMINISTRATION

Recommended dosage

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

In the pivotal efficacy Study 303, 400 mg twice daily dose of LIVTENCITY was administered for 8 weeks (see 5.1 PHARMACODYNAMIC PROPERTIES/CLINICAL TRIALS).

Dose adjustment when co-administered with anti-convulsants

If LIVTENCITY is co-administered with carbamazepine, adjust the dosage of LIVTENCITY to 800-1200 mg twice daily (see 4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION).

If LIVTENCITY is co-administered with phenytoin or phenobarbital, increase the dosage of LIVTENCITY to 1200 mg twice daily (see 4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION).

Special patient populations

Elderly patients

No dose adjustment is required for patient over 65 years of age.

Paediatric patients

The safety and efficacy of LIVTENCITY in patients below 18 years of age have not been established.

Renal impairment

No dose adjustment of LIVTENCITY is needed 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 (see 5.2 PHARMACOKINETIC PROPERTIES).

Hepatic impairment

No dose adjustment of LIVTENCITY is needed 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 (see 5.2 PHARMACOKINETIC PROPERTIES).

Method 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 whole, dispersed, or crushed tablets by mouth, or as dispersed tablets through a polyvinyl chloride (PVC) or polyurethane nasogastric or orogastric tube (French size 10 or larger). The suspension may be prepared ahead of time and stored at room temperature for up to 8 hours.

Administration of dispersed or crushed tablets by mouth:

1. Place the appropriate number of tablets for the prescribed dose into a suitable container. If desired, the tablets may be crushed. Add the appropriate volume of drinking water (other liquids have not been tested) to make a suspension (see Table 1).
2. Swirl the container gently to keep the particles from settling and administer the suspension before it settles.
3. Rinse the container with 15 mL of drinking water and administer the rinsed water.

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

| Recommended Dosage | Number of 200 mg Tablets | Volume of Drinking Water |
|--------------------|--------------------------|--------------------------|
| 400 mg | Two | 30 mL |
| 800 mg | Four | 60 mL |
| 1200 mg | Six | 90 mL |

4. Repeat Step 3. Visually confirm that no particles are left in the container. If particles remain, repeat Step 3.

Administration of dispersed tablets through a nasogastric (NG) or orogastric (OG) tube:

1. Remove the plunger out of a 50- or 60-mL syringe. Add two tablets into the syringe body and place the plunger back in the syringe.
2. Withdraw 30 mL of drinking water (other liquids have not been tested) into the syringe and hold the syringe with the tip pointing upward. Pull the plunger further to a higher volume position to have some air space in the syringe. Shake the syringe well (careful not to spill the contents) for about 30 to 45 seconds or until the tablets are completely dispersed.
3. Once the tablets are completely dispersed in the syringe, attach the syringe to the NG or OG tube and administer the dispersion before it settles.
4. Withdraw 15 mL of water using the same syringe and flush through the same NG or OG tube.
5. Repeat Step 4 and make sure no particles are left in the syringe by visual inspection. If particle remain, repeat Step 4.

For recommended doses of 800 mg and 1200 mg (see Table 1), repeat Steps 1-5, two or three times accordingly. The same syringe, NG or OG tube can be used.

4.3 CONTRAINDICATIONS

LIVTENCITY is contraindicated in individuals with known hypersensitivity to maribavir or any components of the formulation (see excipients listed in section 6.1).

Co-administration of LIVTENCITY with ganciclovir or valganciclovir is contraindicated.

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 4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION and 5.2 PHARMACOKINETIC PROPERTIES).

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. Monitor CMV DNA levels and check for resistance if patient does not

respond to treatment. Some maribavir pUL97 resistance-associated substitutions confer cross-resistance to ganciclovir and valganciclovir.

Patients with CMV central nervous system (CNS) infection

LIVTENCITY was not studied in patients with CMV CNS infection. 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 5.2 PHARMACOKINETIC PROPERTIES). The efficacy of LIVTENCITY for the treatment of CMV retinitis has not been established. Therefore, LIVTENCITY is not expected to be effective in treating CMV CNS infections (e.g., meningo-encephalitis, retinitis).

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 2 for steps to prevent or manage these known or potentially significant medicinal product interactions, including dosing recommendations (see 4.3 CONTRAINDICATIONS and 4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION).

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, cyclosporin, sirolimus, and everolimus). Frequently monitor immunosuppressant drug levels throughout treatment with LIVTENCITY, especially following initiation and after discontinuation of LIVTENCITY and adjust the dose, as needed (see 4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION and 4.8 UNDESIRABLE EFFECTS and 5.2 CLINICAL PHARMACOKINETICS).

Sodium content

LIVTENCITY contains less than 1 mmol sodium (23 mg) per tablet, essentially, 'sodium-free'.

Use in the elderly

No dose adjustment is required for patient over 65 years of age.

Paediatric use

The safety and efficacy of LIVTENCITY in patients below 18 years of age have not been established.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 5.2 Pharmacokinetic Properties). Concomitant administration of strong CYP3A inducers, such as rifampicin, rifabutin, and St John's wort, should be avoided, as significant decreases in maribavir plasma concentrations may occur which may result in decrease in efficacy. Alternative antimicrobial or anti-tuberculosis therapy with a lower CYP3A induction potential should be considered (see 5.2 PHARMACOKINETIC PROPERTIES).

Co-administration with carbamazepine, phenobarbital, and phenytoin (strong or moderate CYP3A inducers) is likely to decrease maribavir concentrations, and therefore, the maribavir dose should be increased according to Table 2 (see 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.2 PHARMACOKINETIC PROPERTIES).

Co-administration of maribavir with other strong or moderate CYP3A inducers has not been evaluated, but decreased maribavir concentrations are expected. If co-administration with other strong or moderate CYP3A inducers cannot be avoided, a maribavir dose increase up to 1200 mg twice daily should be considered (see 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.2 PHARMACOKINETIC PROPERTIES).

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

Effect of maribavir on other medicinal products

Maribavir is contraindicated with valganciclovir/ganciclovir. Maribavir may antagonize 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 4.3 CONTRAINDICATIONS and 5.1 PHARMACODYNAMIC PROPERTIES).

At therapeutic concentrations, clinically significant interactions are not expected when maribavir is co-administered with substrates of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2E1, 2D6, and 3A4; UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B7; bile salt export pump (BSEP); multidrug and toxin extrusion protein (MATE)1/2K; organic anion transporters (OAT)1 and OAT3; organic cation transporters (OCT)1 and OCT2; organic anion transporting polypeptide (OATP)1B1 and OATP1B3 based on *in vitro* and clinical drug interaction results (see Table 2 and 5.2 PHARMACOKINETIC PROPERTIES) except the following medicinal products. *In vitro*, Breast Cancer Resistance Protein (BCRP) indicated higher potential for drug interactions with drugs transported by this transporter at clinically relevant concentrations. The primary metabolite VP44469 was not a CYP inhibitor at clinically relevant concentrations.

Co-administration of maribavir increased plasma concentrations of immunosuppressants, including tacrolimus (see Table 2). When the immunosuppressants tacrolimus, cyclosporin, everolimus, or sirolimus are co-administered with maribavir, frequently monitor immunosuppressant drug levels throughout treatment with maribavir, especially following initiation and after discontinuation of maribavir and adjust dose, as needed (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Table 2).

Co-administration of maribavir with rosuvastatin, a sensitive BCRP substrate, is expected to increase rosuvastatin concentration. Rosuvastatin is associated with the occurrence of myopathy and rhabdomyolysis (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Table 2).

Maribavir inhibited P-gp transporter *in vitro* at clinically relevant concentrations. In a clinical study, co-administration of LIVTENCITY increased plasma concentrations of digoxin (see Table 2). Therefore, caution should be exercised when LIVTENCITY and sensitive P-gp substrates (e.g., digoxin) are co-administered. Serum digoxin concentrations should be monitored, and dose of digoxin may need to be reduced, as needed (see Table 2).

General information

If dose adjustments of concomitant medicinal products are made due to treatment with LIVTENCITY, doses should be readjusted after treatment with LIVTENCITY is completed. Table 2 provides a listing of established 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 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 5.2 PHARMACOKINETIC PROPERTIES).

Table 2: 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 |
|--|---|---|
| Acid-Reducing Agents | | |
| 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 _{max} 0.84 (0.75, 0.94) | No dose adjustment is required. |
| famotidine | Interaction not studied. Expected: ↔ maribavir | No dose adjustment is required. |
| omeprazole | ↔ maribavir ↑ plasma omeprazole/5-hydroxyomeprazole concentration ratio 1.71 (1.51, 1.92) (CYP2C19 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 |
|--|--|---|
| pantoprazole | Interaction not studied. Expected: ↔ maribavir | No dose adjustment is required. |
| Anti-arrhythmics | | |
| digoxin (0.5 mg single dose, 400 mg twice daily maribavir) | ↔ 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. 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. |
| Anti-convulsants | | |
| carbamazepine | Interaction not studied. Expected: ↓ maribavir (CYP3A induction) | A dose adjustment of maribavir to 800-1200 mg twice daily is recommended when co-administration with carbamazepine. |
| phenobarbital | Interaction not studied. Expected: ↓ maribavir (CYP3A induction) | A dose adjustment of maribavir to 1200 mg twice daily is recommended when co-administration with phenobarbital. |
| phenytoin | Interaction not studied. Expected: ↓ maribavir (CYP3A induction) | A dose adjustment of maribavir to 1200 mg twice daily is recommended when co-administration with phenytoin. |
| Anti-inflammatories | | |
| sulfasalazine | Interaction not studied. Expected: ↑ sulfasalazine (BCRP inhibition) | No dose adjustment is required. |
| Anti-fungals | | |
| 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 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. |

| Medicinal Product by Therapeutic Area | Effect on Geometric Mean Ratio (90 % CI) (likely mechanism of action) | Recommendation Concerning Co-administration with maribavir |
|---|---|--|
| | C_{max} 1.00 (0.87, 1.15) (CYP2C19 inhibition) | |
| Anti-hypertensives | | |
| diltiazem | Interaction not studied. Expected: ↑ maribavir (CYP3A inhibition) | No dose adjustment is required. |
| Anti-mycobacterials | | |
| 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. |
| 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 potential for a decrease in efficacy of maribavir. |
| Anti-tussives | | |
| dextromethorphan (30 mg single dose, maribavir 400 mg twice daily) | ↔ dextrophan 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 | | |
| 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 potential for a decrease in efficacy of maribavir. |
| HMG-CoA Reductase Inhibitors | | |
| atorvastatin fluvastatin simvastatin | Interaction not studied. Expected: ↑ HMG-CoA reductase inhibitors (BCRP inhibition) | 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. |

| Medicinal Product by Therapeutic Area | Effect on Geometric Mean Ratio (90 % CI) (likely mechanism of action) | Recommendation Concerning Co-administration with maribavir |
|---|---|--|
| Immunosuppressants | | |
| cyclosporin ^a everolimus ^a sirolimus ^a | Interaction not studied. Expected: ↑ cyclosporin, everolimus, sirolimus (CYP3A/P-gp inhibition) | Frequently monitor cyclosporin, everolimus and sirolimus levels, especially following initiation and after discontinuation of LIVTENCITY and adjust dose, as needed. |
| tacrolimus ^a | ↑ 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) | Frequently monitor tacrolimus levels, especially following initiation and after discontinuation of LIVTENCITY and adjust dose, 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) | No dose adjustment is required. |
| Sedatives | | |
| midazolam (0.075 mg/kg single oral dose, maribavir 400 mg twice daily) | ↔ midazolam AUC 0.89 (0.79,1.00) C _{max} 0.82 (0.70, 0.96) | No dose adjustment is required. |

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

*AUC_{0-∞} for single dose, AUC₀₋₁₂ for twice daily dose daily.

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

^a Refer to the respective product information.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Fertility studies were not conducted in humans with maribavir. 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 ≥ 100 mg/kg/day [which is estimated to be less than the human exposure at the recommended human dose (RHD)]. Although an increase in testes weight was observed in the 6-month repeat-dose toxicity study in rats and a decrease observed in the combined fertility and embryofetal development study, neither were accompanied with any microscopic changes and were not considered adverse. There were no effects on female reproductive organs in rats and no effects either in males or female monkeys.

Use in pregnancy

Category D

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

Maribavir had no effect on embryo-fetal growth or development at dose levels up to 400 mg/kg/day, at exposures similar to those observed in humans at the RHD.

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

In the pre- and postnatal developmental toxicity study maribavir was administered to pregnant rats at oral doses of 50, 150, or 400 mg/kg/day from GD 7 to postnatal day (PND) 21. A delay in developmental milestones was observed, including pinna detachment at doses ≥ 150 mg/kg/day and eye opening and preputial separation associated with reduced bodyweight gain of the offspring at 400 mg/kg/day. In addition, decreased fetal survival and litter loss was observed due to maternal toxicity and poor maternal care, respectively, at doses ≥ 150 mg/kg/day. No effects were observed at 50 mg/kg/day (which is estimated to be less than the human exposure at the RHD). No effects on number of offspring, proportion of males, number of live pups, or survival to PND 4 were observed at any dose in the offspring born to the second generation. Maribavir is not recommended during pregnancy and in women of childbearing potential not using contraception.

Use in lactation.

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 maribavir.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

LIVTENCITY has no influence on the ability to drive and use machines. LIVTENCITY may cross the blood-brain barrier in humans, but CNS penetration is expected to be low compared to plasma levels.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial experience

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 (IAT) consisting of monotherapy or dual therapy with ganciclovir, valganciclovir, foscarnet, or cidofovir (N=117) for an 8-week treatment phase following a diagnosis of resistant/refractory CMV. Adverse events were collected during the treatment phase and follow up phase through Study Week 20. The mean exposures (SD) for LIVTENCITY were 48.6 (13.82) days. LIVTENCITY treated patients received treatment a maximum of 60 days. The most common adverse events occurring in more than 10% of subjects in the LIVTENCITY, ganciclovir/valganciclovir or foscarnet are outlined in Table 3.

Table 3: Adverse Events (All Grades) Reported in > 10% of Patients Receiving LIVTENCITY, ganciclovir/valganciclovir or foscarnet in Study 303

| Adverse Event | LIVTENCITY (N=234) (%) | Ganciclovir/valganciclovir (N=56) (%) | Foscarnet (N=47) (%) |
|--------------------------------|------------------------------|---|----------------------------|
| Taste disturbance ^a | 46 | 4 | 2 |
| Nausea | 21 | 14 | 30 |
| Diarrhea | 19 | 23 | 19 |
| Vomiting | 14 | 13 | 17 |
| Anaemia | 12 | 7 | 19 |
| Fatigue | 12 | 13 | 6 |
| Pyrexia | 10 | 11 | 19 |
| Neutropenia | 9 | 34 | 15 |
| Acute kidney injury | 9 | 2 | 21 |
| Headache | 8 | 11 | 17 |
| Oedema peripheral | 7 | 5 | 11 |
| Hypomagnesemia | 4 | 4 | 15 |
| Hypertension | 4 | 2 | 13 |
| Hypokalaemia | 3 | 2 | 19 |
| Leukopenia | 3 | 13 | 2 |

^a taste disturbance includes the following reported preferred terms: ageusia, dysgeusia, hypogeusia and taste disorder

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 occurring at < 1%.

Treatment-emergent serious adverse events (SAEs) considered related to study-assigned treatment occurred less frequently in the LIVTENCITY group than in the IAT group (5.1% and 14.7% respectively). No patients in the LIVTENCITY group experienced serious, drug-related neutropenia or febrile neutropenia. In contrast in patients treated with ganciclovir/valganciclovir, 4% of patients had serious related neutropenia and 7% had serious related febrile neutropenia. In addition, 1% of patients in the LIVTENCITY group and 11% in the foscarnet group experienced serious related renal disorders (acute kidney injury and renal impairment).

The following convention is used for the classification of the frequency of an adverse drug reaction (ADR) and is based on the Council for International Organizations of Medical Sciences (CIOMS) guidelines: 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 $< 1/1,000$); very rare ($< 1/10,000$).

Table 4: Adverse Drug Reactions Associated with LIVTENCITY

| System Organ Class | Frequency | Adverse Reactions |
|--|-------------|--|
| Nervous system disorders | Very Common | Taste disturbance ^a |
| | Common | Headache |
| Gastrointestinal disorders | Very Common | Diarrhoea, nausea, vomiting |
| | Common | Abdominal pain upper |
| General disorders and administration site conditions | Very Common | Fatigue |
| | 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 (comprising 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 resolved either while patients remained on therapy (37%) or within a median of 7 days (Kaplan-Meier estimate, 95% CI: 4-8 days) after treatment discontinuation.

Immunosuppressant Drug Level Increase

Immunosuppressant drug level increase was reported as an adverse event in 9% of patients treated with LIVTENCITY. LIVTENCITY has the potential to increase the drug concentrations of immunosuppressant drugs that are CYP3A/ P-gp substrates with narrow therapeutic ranges (including tacrolimus, cyclosporin, sirolimus and everolimus). Frequently monitor immunosuppressant drug levels throughout treatment with LIVTENCITY, especially following initiation and after discontinuation of LIVTENCITY and adjust the dose, as needed (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION and 5.2 PHARMACOKINETIC PROPERTIES).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at

www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

In Study 303, an accidental overdose of a single extra dose occurred in one LIVTENCITY treated subject on Day 13 (1200 mg total daily dose). No adverse reactions were reported.

In Study 202, patients were treated with up to 1200 mg twice daily for up to 24 weeks of treatment. The safety profile of higher doses and longer durations were comparable to 400 mg twice daily. However, the highest dose was associated with a greater incidence of immunosuppressant drug level increased.

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

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 the phosphorylation of proteins; an effect achieved at low concentrations of maribavir.

Antiviral activity

Maribavir selectively inhibited *in vitro* HCMV replication in yield reduction, DNA hybridization, and plaque reduction assays in human cell lines at noncytotoxic sub-micromolar concentrations. The EC₅₀ values ranged from 0.03 to 2.2 µM depending on the cell line and assay endpoint.

The cell culture antiviral activity of maribavir has also been evaluated against CMV clinical isolates. The mean EC₅₀ values were 0.08 µM (n=10, range 0.03-0.13 µM) and 0.31 µM (n=10, range 0.12-0.56 µM) using DNA hybridization and plaque reduction assays, respectively.

Maribavir is highly selective for human CMV. There is no significant difference in baseline maribavir EC₅₀ values across the four human CMV glycoprotein B genotypes.

Combination antiviral activity

When maribavir was tested in combination with other antiviral compounds, it showed additive interactions with letermovir, foscarnet, cidofovir, and GW275175X (a benzimidazole CMV terminase inhibitor) against wild type and mutant human CMV, strong antagonism with ganciclovir, and strong synergy with the mechanistic target of rapamycin (mTOR) inhibitor sirolimus.

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, L397R, T409M, H411L/N/Y, and C480F. These mutations confer resistance that ranges from 3.5-fold to >200-fold increase in EC₅₀ 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 EC₅₀).

In clinical studies

In Phase 2 Study 202 and Study 203 evaluating maribavir in 279 hematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT) recipients, post-treatment pUL97 genotyping data from 23 of 29 patients who initially achieved viremia 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 EC₅₀ compared with the wild-type strain. The pUL27 mutation G344D was not shown to confer maribavir resistance.

In Phase 3 Study 303, 60/234 patients (25.6%) were identified with treatment-emergent mutations in pUL97 that confer resistance to maribavir: C480F, F342Y, H411N, H411Y, T409M, F342Y+H411Y, F342Y+T409M+H411N, H411Y+C480F, T409M+C480F, T409M+H411Y, H411L+H411Y+C480F, H411N+C480F. Treatment-emergent mutations in pUL97 were identified in 43.2% of subjects (60/139) who had post-baseline genotyping performed after detection of a CMV DNA viral load above a pre-defined cut-off level of ≥ 500 copies/mL (455 IU/mL).

Cross resistance

There is clinical evidence of cross-resistance to maribavir and ganciclovir/valganciclovir at UL97: F342Y- 4.5-fold and 6.0-fold increase in EC₅₀ to maribavir and ganciclovir, respectively; and C480F- 224-fold and 2.3-fold increase in EC₅₀ to maribavir and ganciclovir, respectively. The prevalence of F342Y, the only cross-resistant mutation present in Study 303 subjects prior to maribavir treatment, was low (3/309 subjects with baseline UL97 genotyping).

Pharmacodynamic effects

Cardiac electrophysiology

The effect of maribavir at doses up to 1200 mg on the QTc interval was evaluated in a randomised, single dose, placebo and active controlled (moxifloxacin 400 mg oral) 4 period

crossover through QT trial in 52 healthy subjects. Maribavir does not prolong QTc 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 trials

LIVTENCITY was evaluated in a Phase 3, multicentre, randomised, open-label, active controlled superiority study (Study 303) to assess the efficacy and safety of LIVTENCITY treatment compared to 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.

Patients were stratified by transplant type (HSCT or SOT) and screening viral load and then randomised in a 2:1 allocation 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.

Table 5: Summary of the Demographic and Disease Characteristics of the Study Population in Study 303

| Characteristic ^a | LIVTENCITY 400 mg Twice Daily (N=235) | IAT (N=117) |
|--|---|----------------|
| Age (years)^b | | |
| Median | 57 | 54 |
| Min, Max | 19, 79 | 19, 77 |
| Sex, n (%) | | |
| Male | 148 (63) | 65 (56) |
| Female | 87 (37) | 52 (44) |
| Ethnicity, n (%) | | |
| Hispanic or Latino | 14 (6) | 7 (6) |
| Not Hispanic or Latino | 198 (84) | 95 (81) |
| Not reported | 19 (8) | 12 (10) |
| Unknown | 4 (2) | 3 (3) |
| Race, n (%) | | |
| White | 179 (76) | 87 (74) |
| Asian | 9 (4) | 7 (6) |
| Black or African American | 29 (12) | 18 (15) |
| Other | 16 (7) | 5 (4) |
| Missing | 2 (1) | 0 |
| IAT treatment | | |
| Foscarnet | n/a | 47 (41) |
| Ganciclovir/ Valganciclovir | n/a | 56 (48) |
| Cidofovir | n/a | 6 (5) |
| Foscarnet + Ganciclovir/Valganciclovir | n/a | 7 (6) |
| Transplant type, n (%) | | |
| HSCT | 93 (40) | 48 (41) |
| SOT ^c | 142 (60) | 69 (59) |
| Kidney ^f | 74 (52) | 32 (46) |
| Lung ^f | 40 (28) | 22 (32) |
| Heart ^f | 14 (10) | 9 (13) |

| Characteristic ^a | LIVTENCITY 400 mg Twice Daily | IAT |
|---|----------------------------------|----------|
| Multiple ^f | 5 (4) | 5 (7) |
| Liver ^f | 6 (4) | 1 (1) |
| Pancreas ^f | 2 (1) | 0 |
| Intestine ^f | 1 (1) | 0 |
| CMV DNA levels category as reported by central laboratory, n (%)^d | | |
| High | 14 (6) | 7 (6) |
| Intermediate | 68 (29) | 25 (21) |
| Low | 153 (65) | 85 (73) |
| Baseline symptomatic CMV infection | | |
| No | 214 (91) | 109 (93) |
| Yes ^e | 21 (9) | 8 (7) |
| CMV syndrome (SOT only), n (%) ^{e, f, g} | 10 (48) | 7 (88) |
| Tissue Invasive disease, n (%) ^{e, f, g} | 12 (57) | 1 (13) |

CMV=cytomegalovirus, DNA=deoxyribonucleic acid, HSCT=hematopoietic stem cell transplant, IAT=investigator assigned anti-CMV treatment, max=maximum, min=minimum, N=number of patients, , n/a not applicable, SD=standard deviation, SOT=solid organ transplant

^a 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.

^b Age was calculated as the difference between date of birth and date of informed consent, truncated to years.

^c The most recent transplant

^d 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).

^e Confirmed by Endpoint Adjudication Committee (EAC)

^f Percentages are based on the number of patients within the category.

^g Patients could have CMV syndrome and tissue invasive disease.

The primary efficacy endpoint was confirmed CMV viremia clearance (plasma CMV DNA concentration below the lower limit of quantification ($< \text{LLOQ}$; i.e., < 137 IU/mL) as assessed by COBAS® AmpliPrep/COBAS® TaqMan® CMV test) at Week 8. The key secondary endpoint was CMV viremia clearance and CMV infection symptom control at the end of Study Week 8 with maintenance of this treatment effect through Study Week 16.

For the primary endpoint, LIVTENCITY was superior to IAT (56% vs. 24%, respectively). For the key secondary endpoint, 19% vs 10% achieved both CMV viremia clearance and CMV infection symptom control in the LIVTENCITY and IAT group, respectively (see Table 6).

Table 6: Primary and Key Secondary Efficacy Endpoint Analysis (Randomised Set) in Study 303

| | LIVTENCITY 400 mg Twice Daily (N=235) n (%) | IAT (N=117) n (%) |
|---|--|-------------------------|
| Primary Endpoint: CMV Viremia Clearance Response at Week 8 | | |
| Overall | | |
| Responders | 131 (56) | 28 (24) |
| Adjusted difference in proportion of responders (95% CI) ^a | 32.8 (22.8, 42.7) | |
| p-value: adjusted ^a | < 0.001 | |

| | LIVTENCITY 400 mg Twice Daily (N=235) n (%) | IAT (N=117) n (%) |
|---|--|----------------------------------|
| Key Secondary Endpoint: Achievement of CMV Viremia Clearance and CMV Infection Symptom Control^c at Week 8, With Maintenance Through Week 16^b | | |
| Overall | | |
| Responders | 44 (19) | 12 (10) |
| 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; IAT=investigator-assigned anti-CMV treatment; N=number of patients.

^a Cochran-Mantel-Haenszel weighted average approach was used for the adjusted difference in proportion (maribavir – IAT), the corresponding 95% CI, and the p-value after adjusting for the transplant type and baseline plasma CMV DNA concentration. Only those with both stratification factors were included in the computation.

^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 summarized in Table 7.

Table 7: Analysis of Failures for Primary Efficacy Endpoint

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

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

Percentages are based on the number of subjects in the 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 [ie, <137 IU/mL]).

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

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

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

The treatment effect was consistent across key subgroups and supports the generalizability of the study outcomes (see Table 8).

Table 8: Percentage of Responders by Subgroup in Study 303

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

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

Recurrence

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

Rescue arm

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

Effect on mortality

In pivotal study 303, the number of deaths reported was 14/235 (6.0%) in maribavir group compared with 5/116 (4.3%) within 8 weeks of observation. The number of reported deaths within 20 weeks of observation was 25/235 (10.7%) in maribavir group and 11/116 (9.5%) in IAT group.

Phase 2 studies

Study 202 was a Phase 2, randomised study to assess the safety and anti-CMV activity of 400 mg, 800 mg, and 1200 mg twice daily of LIVTENCITY for the treatment of 120 transplant recipients with CMV infections that are resistant or refractory to treatment with ganciclovir/valganciclovir or foscarnet. By Week 6, 28/40 (70%) patients receiving 400 mg twice daily had achieved confirmed undetectable plasma CMV DNA. The mean (SD) exposure to patients receiving 400 mg LIVTENCITY-treated patients was 85 (55) days with a maximum of 177 days. The virologic response of doses of 400 mg, 800 mg, or 1200 mg twice daily of LIVTENCITY were comparable within 6 weeks.

Study 203 was a Phase 2, randomised, dose-ranging study to assess the safety and anti-CMV activity of 400 mg, 800 mg, and 1200 mg twice daily LIVTENCITY versus valganciclovir for the pre-emptive treatment of 159 SOT or HSCT recipients with CMV infection without CMV organ disease or resistant/refractory CMV infection.

By Weeks 3 and 6, 26/40 (65%) and 31/40 (78%) patients receiving 400 mg twice daily had achieved confirmed undetectable plasma CMV DNA compared to 22/40 (55%) and 26/40 (65%) patients receiving valganciclovir, respectively. The mean (SD) exposure to patients receiving 400 mg of LIVTENCITY was 50 (29) days with a maximum of 92 days. The virologic response of doses up to 1200 mg twice daily and durations of up to 12 weeks of LIVTENCITY were comparable.

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.

5.2 PHARMACOKINETIC PROPERTIES

Maribavir pharmacological activity is due to the parent drug. The pharmacokinetics of maribavir have been characterised following oral administration in healthy subjects and transplant patients. Maribavir exposure increased in approximately dose proportionally. In healthy subjects, the geometric mean steady state AUC_{0-τ}, C_{max}, and C_{trough} values were 101 µg*h/mL, 16.4 µg/mL, and 2.89 µg/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_{max}.

The pharmacokinetic properties of maribavir following administration of LIVTENCITY are displayed in Table 9. The multiple-dose pharmacokinetic parameters are provided in Table 10.

Table 9: Pharmacokinetic Properties of Maribavir

| | |
|-------------------------------|------------|
| Absorption^a | |
| T _{max} (h), median | 1.0 to 3.0 |
| Distribution | |

| | |
|--|--|
| Mean apparent steady-state volume of distribution (V_{ss} , L) | 24.9 |
| % bound to human plasma proteins | 98.0 across the concentration range of 0.05-200 $\mu\text{g/mL}$ |
| Blood-to plasma ratio | 1.37 |
| Elimination | |
| Major route of elimination | Hepatic metabolism |
| Half-life ($t_{1/2}$) in transplant patients (h), mean | 4.32 |
| Oral clearance (CL/F) in transplant patients (L/h), mean | 2.67 |
| Metabolism | |
| Metabolic pathways ^b | CYP3A4 (major) and CYP1A2 (minor) |
| Excretion | |
| % of dose excreted as total ^{14}C (unchanged drug) in urine ^c | 61 (<2) |
| % of dose excreted as total ^{14}C (unchanged drug) in feces ^c | 14 (5.7) |

^a When taken orally with a high fat high caloric meal versus fasted, the $\text{AUC}_{0-\infty}$ and C_{max} (geometric mean ratio [90% CI] of maribavir are 0.878 [0.843, 0.915] and 0.716 [0.671, 0.764], respectively.

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

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

Table 10: Multiple-Dose Pharmacokinetic Parameters of Maribavir

| Parameter GM (% CV) | $\text{AUC}_{0-\tau}$ $\mu\text{g}\cdot\text{h/mL}$ | C_{max} $\mu\text{g/mL}$ | C_{trough} $\mu\text{g/mL}$ |
|------------------------------|--|---|--|
| 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

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 H2 receptor antagonists (H2 blockers), or antacids.

The intrasubject variability (< 22%) and inter-subject 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 high fat, high caloric meal did not have any statistically significant effect on the overall exposure (AUC) and resulted in 28% decrease in C_{max} of maribavir. Maribavir can be administered orally with or without food as has been done in the clinical studies.

Distribution

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 can penetrate the blood-retinal barrier and may cross the blood-brain barrier, but CNS penetration is expected to be low compared to plasma levels (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Metabolism

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 UGT1A1/1A3/2B7 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.

In *in vitro* studies, metabolism of maribavir is not mediated by CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A5, UGT1A4, UGT1A6, UGT1A10, or UGT2B15.

Special Populations

Impaired renal function

No clinically significant effect of mild/moderate (CL_{cr}, between 30 and 80 mL/min) or severe (CL_{cr} less than 30 mL/min) renal impairment 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 less than 9%.

Impaired hepatic function

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_{max} were 26% and 35% higher, respectively, in subjects with moderate hepatic impairment.

Age, gender, race, ethnicity, weight, and transplant type

Age (18-79 years), gender, race (Caucasian, Black, Asian, or others), ethnicity (Hispanic/Latino or non-Hispanic/Latino) body weight (36 to 141 kg) and transplant type 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

Carcinogenicity

Two-year carcinogenic studies were conducted in both mice and rats at doses up to 150 and 100 mg/kg/day, respectively. 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 there was an equivocal elevation in the incidence of hemangioma, hemangiosarcoma, and combined hemangioma/hemangiosarcoma. The incidence in the treatment arm (12.9%) only marginally exceeded the reported historical control values of 12 % at Charles Rivers laboratories and up to 8.3% at Covance laboratories (now LabCorp) in mice of similar strain. In female mice there was also an equivocal increase in the incidence of adenocarcinoma and combined adenoma/adenocarcinoma of the uterus in the 150 mg/kg/day group but is unlikely to be test article related as the incidence (4% increase for adenomas) was within historical control values (4.29%) observed in the laboratory. The incidence of both tumours showed borderline significant trends.

Genotoxicity

Maribavir was not mutagenic in a bacterial mutation assay. In the mouse lymphoma assay, maribavir demonstrated mutagenic potential in the absence of metabolic activation and the results were equivocal in the presence of metabolic activation (not concentration-dependent and not reproduced in the repeat assay). Maribavir was not clastogenic in the *in vivo* rat bone marrow micronucleus assay up to very high dose of 1200 mg/kg that was toxic and close to producing lethality. Given the negative results of the *in vivo* rat micronucleus assay the weight of evidence indicates that maribavir does not exhibit genotoxic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core:

Magnesium stearate
Microcrystalline cellulose
Sodium starch glycolate

Film coating:

Brilliant blue FCF aluminium lake (FD&C Blue #1)
Macrogol (polyethylene glycol)
Polyvinyl alcohol
Purified talc
Titanium dioxide

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Do not freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

High-density polyethylene (HDPE) bottles with child resistant cap. Pack sizes of 28 or 56 film-coated tablets.

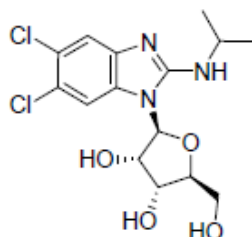
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



The molecular formula for maribavir is $C_{15}H_{19}Cl_2N_3O_4$ and its molecular weight is 376.24 g/mol.

CAS number

176161-24-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

8 SPONSOR

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Telephone: 1800 012 612

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9 DATE OF FIRST APPROVAL

7 October 2022

10 DATE OF REVISION

24 September 2024

SUMMARY TABLE OF CHANGES

| Section Changed | Summary of new information |
|-----------------|---|
| 4.2 | New text added under the new heading 'Dose adjustment when co-administered with anti-convulsants' |
| 4.4 | Revised the CNS CMV precaution statement |
| 4.5 | Additional information on concomitant use of maribavir with P-gp substrates |
| 4.7 | Revised statement on 'the effect of ability to drive and use machines' |
| 5.1 | Addition of more comprehensive description of the cell culture analysis; revision of numbers of subjects and mutations in viral resistance |
| 5.2 | Update of pharmacokinetic properties of maribavir: distribution, elimination, metabolism, effect of food and transplant type |
| All | Editorial changes: texts consolidated to a table format, and subsequent tables re-numbered and typographical error corrections throughout the document. |
| | |
| | |

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