▼ This medicine 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 https://www.tga.gov.au/reporting-problems

AUSTRALIAN PRODUCT INFORMATION – PREVYMIS® (letermovir)

1. NAME OF THE MEDICINE

Letermovir

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PREVYMIS tablets and concentrated injection for infusion contain letermovir.

Film coated tablet
Each film-coated tablet contains 240 mg or 480 mg of letermovir.
Excipients with known effect
Each 240 mg film-coated tablet contains 3.96 mg of lactose (as monohydrate) and 1.90 mg (or 0.08 mmol) of sodium.
Each 480 mg film-coated tablet contains 6.38 mg of lactose (as monohydrate) and 3.80 mg (or 0.17 mmol) of sodium.
For the full list of excipients, see section 6.1, LIST OF EXCIPIENTS.

Concentrated injection for infusion
Each single-dose vial contains 240 mg (12 mL per vial) or 480 mg (24 mL per vial) of letermovir.

Excipient with known effect
Each 240 mg vial contains 22.91 mg (or 1.00 mmol) sodium. Each 480 mg vial contains 45.82 mg (or 1.99 mmol) sodium.

For the full list of excipients, see section 6.1, LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

Film coated tablet
PREVYMIS 240 mg tablet is a yellow oval tablet. Each tablet is debossed with “591” on one side and MSD logo on the other side.

PREVYMIS 480 mg tablet is a pink oval, bi-convex tablet. Each tablet is debossed with “595” on one side and MSD logo on the other side.

Concentrated injection for infusion
PREVYMIS 240 mg/12 mL (20 mg/mL) concentrated injection for infusion is supplied as a clear solution and may contain a few small translucent or white particles in a single-dose vial.

PREVYMIS 480 mg/24 mL (20 mg/mL) concentrated injection for infusion is supplied as a clear solution and may contain a few small translucent or white particles in a single-dose vial.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

CMV Prophylaxis in Haematopoietic Stem Cell Transplant (HSCT) Recipients
PREVYMIS is indicated for the prophylaxis of cytomegalovirus (CMV) infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant.

CMV Prophylaxis in Kidney Transplant Recipients
PREVYMIS is indicated for the prophylaxis of CMV disease in adult kidney transplant recipients at high risk (Donor CMV seropositive/Recipient CMV seronegative [D+/R-]).

4.2 DOSE AND METHOD OF ADMINISTRATION

Recommended Dosage in Adults
The recommended dosage of PREVYMIS is 480 mg administered once daily.

HSCT
PREVYMIS should be started after HSCT. PREVYMIS may be started on the day of transplant and no later than 28 days post-HSCT. PREVYMIS may be started before or after engraftment. Continue PREVYMIS through 100 days post-HSCT. In patients at risk for late CMV infection and disease, PREVYMIS may be continued through 200 days post-HSCT.

Kidney Transplant
PREVYMIS should be started on the day of transplant and no later than 7 days post-kidney transplant and continued through 200 days post-transplant.

Important Dosing and Administration Information
PREVYMIS Film coated tablets
- Administer with or without food.
- Swallow tablets whole. Do not divide, crush or chew.

PREVYMIS Concentrated injection for infusion
- PREVYMIS injection must be administered through a sterile 0.2 micron or 0.22 micron polyethersulfone (PES) in-line filter.
- Administer by intravenous infusion via a peripheral catheter or central venous line over approximately 60 minutes.
- Do not administer as an intravenous bolus injection.

PREVYMIS tablet and concentrated injection for infusion may be used interchangeably at the discretion of the physician, and no dose adjustment is necessary.

Dosage Adjustment in Adults
- If PREVYMIS is co-administered with ciclosporin, the dosage of PREVYMIS should be decreased to 240 mg once daily [see Table 1 in section 4.5, INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS].
- If ciclosporin is initiated after starting PREVYMIS, the next dose of PREVYMIS should be decreased to 240 mg once daily.
- If ciclosporin is discontinued after starting PREVYMIS, the next dose of PREVYMIS should be increased to 480 mg once daily.
- If ciclosporin dosing is temporarily interrupted due to high ciclosporin levels, no dose adjustment of PREVYMIS is needed.

Missed Dose
Instruct patients that if they miss a dose of PREVYMIS, they should take it as soon as they remember. If they do not remember until it is time for the next dose, instruct them to skip the missed dose and go back to the regular schedule. Instruct patients not to double their next dose or take more than the prescribed dose.

Special populations
Hepatic impairment
No dose adjustment of PREVYMIS is required based on mild (Child-Pugh Class A) to moderate (Child Pugh Class B) hepatic impairment. PREVYMIS is not recommended for patients with severe (Child-Pugh Class C) hepatic impairment [see section 5.2, PHARMACOKINETIC PROPERTIES, Specific Populations].

PREVYMIS is not recommended in patients with moderate hepatic impairment combined with moderate or severe renal impairment [see section 5.2, PHARMACOKINETIC PROPERTIES, Specific Populations].

Renal impairment
No dose adjustment of PREVYMIS is required based on renal impairment [see section 5.2, PHARMACOKINETIC PROPERTIES, Specific Populations].

Elderly
No dose adjustment of PREVYMIS is required based on age [see section 5.2, PHARMACOKINETIC PROPERTIES, Specific Populations].

Paediatric population
The safety and efficacy of PREVYMIS in patients below 18 years of age have not been established [see section 5.2, PHARMACOKINETIC PROPERTIES, Specific Populations].

Preparation and Administration of Intravenous Solution
PREVYMIS concentrated injection for infusion is supplied in 30 mL single-dose vials containing either 240 mg (12 mL per vial) or 480 mg (24 mL per vial). The preparation and administration instructions are the same for either dose.

PREVYMIS vials are for single use in one patient only. Discard any residue.

Preparation
- PREVYMIS must be diluted prior to intravenous (IV) use.
- Inspect vial contents for discoloration and particulate matter prior to dilution. PREVYMIS concentrated injection for infusion is a clear, colorless solution and may contain a few product-related small translucent or white particles.
- Do not use the vial if the solution is cloudy, discolored or contains matter other than a few small translucent or white particles.
- Do not use PREVYMIS concentrated injection for infusion with IV bags and infusion set materials containing polyurethane or the plasticizer diethylhexyl phthalate (DEHP). Materials that are phthalate-free are also DEHP-free.
- Do not shake PREVYMIS vial.
- Add one single-dose vial of PREVYMIS concentrated injection for infusion to a 250 mL pre-filled IV bag containing either 0.9% sodium chloride or 5% dextrose and mix bag gently. Do not shake.
- Once diluted, the solution of PREVYMIS is clear, and ranges from colorless to yellow. Variations of color within this range do not affect the quality of the product.

- The diluted solution should be inspected visually for particulate matter and discoloration prior to administration.
- Discard if the diluted solution is cloudy, discoloured, or contains matter other than a few small translucent or white particles.

Storage of Diluted Solution
- To reduce microbiological hazard, use as soon as practicable after preparation. If storage is necessary, the diluted solution can be stored for up to 24 hours at room temperature or up to 48 hours under refrigeration at 2-8°C.
- This time includes storage of the diluted solution in the intravenous bag through the duration of infusion.

Administration
- The diluted solution must be administered through a sterile 0.2 micron or 0.22 micron PES in-line filter.
- Do not administer the diluted solution through a filter other than a sterile 0.2 micron or 0.22 micron PES in-line filter.
- Administer as an intravenous infusion only. Do not administer as an intravenous push or bolus.
- After dilution, administer PREVYMIS via intravenous infusion via peripheral or central venous catheter using a total time of approximately 60 minutes. Administer the entire contents of the IV bag.

Compatible Diluents, Drug Products, and Other Materials Used for Intravenous Administration

Compatible Diluents

PREVYMIS concentrated injection for infusion is compatible with 0.9% sodium chloride and 5% dextrose solutions.

Compatible Drug Products

A study was conducted to evaluate physical compatibility of PREVYMIS concentrated injection for infusion with injectable drug products. Compatibility was determined through visual observations, turbidity, and measurement of particulate matter. Compatible drug products are listed below.

PREVYMIS should not be co-administered through the same intravenous line (or cannula) with other drug products and diluent combinations except those listed below.

The following compatible drug products may be co-administered with PREVYMIS for injection when both drug products are in 0.9% Sodium Chloride via Y tubing only, as per the approved instructions of the respective drug products.
- Ampicillin sodium
- Ampicillin sodium/Sulbactam sodium
- Anti-thymocyte globulin
- Caspofungin
- Daptomycin
- Fentanyl citrate
- Fluconazole
- Furosemide
- Human insulin
- Magnesium sulfate
- Methotrexate
- Micafungin

The following compatible drug products may be co-administered with PREVYMIS for injection when both drug products are in 5% Dextrose via Y tubing only, as per the approved instructions of the respective drug products.

- Amphotericin B (lipid complex)*
- Anidulafungin
- Cefazolin sodium
- Ceftaroline
- Ceftriaxone sodium
- Doripenem
- Famotidine
- Folic acid
- Ganciclovir sodium
- Hydrocortisone sodium succinate
- Morphine sulfate
- Noradrenaline (norepinephrine) bitartrate
- Pantoprazole sodium
- Potassium chloride
- Potassium phosphate
- Tacrolimus
- Telavancin
- Tigecycline

* Amphotericin B (lipid complex) is compatible with PREVYMIS. However, Amphotericin B (liposomal) is incompatible [see section 6.2 INCOMPATIBILITIES].

Compatible IV Bags and Infusion Set Materials

PREVYMIS is compatible with the following IV bags and infusion set materials. Any IV bags or infusion set materials not listed below should not be used.

IV Bag Materials

Polyvinyl chloride (PVC), ethylene vinyl acetate (EVA) and polyolefin (polypropylene and polyethylene)

Infusion Set Materials

PVC, polyethylene (PE), polybutadiene (PBD), silicone rubber (SR), styrene–butadiene copolymer (SBC), styrene-butadiene-styrene copolymer (SBS), polystyrene (PS)

Plasticizers

Tris (2-Ethylhexyl) trimellitate (TOTM), butyl benzyl phthalate (BBP)

Catheters

Radiopaque polyurethane

4.3 CONTRAINDICATIONS

PREVYMIS is contraindicated in patients with hypersensitivity to letermovir or any of its inactive ingredients.

Pimozide

Concomitant administration of PREVYMIS may result in increased concentrations of pimozide due to inhibition of cytochrome P450 (CYP3A) by letermovir, leading to QT prolongation and torsades de pointes [see section 4.5, INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS].

Ergot alkaloids
Concomitant administration of PREVYMIS may result in increased concentrations of ergot alkaloids (ergotamine and dihydroergotamine) due to inhibition of CYP3A by letermovir, which may lead to ergotism [see section 4.5, INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS].

Ciclosporin with pitavastatin or simvastatin
Concomitant administration of PREVYMIS in combination with ciclosporin may result in significantly increased pitavastatin or simvastatin concentrations, which may lead to myopathy or rhabdomyolysis [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.5, INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS].

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions
The concomitant use of PREVYMIS and certain drugs may result in known or potentially significant drug interactions, some of which may lead to:

- Possible clinically significant adverse reactions from greater exposure of concomitant drugs or PREVYMIS.
- Significant decrease of concomitant drug plasma concentrations which may lead to reduced therapeutic effect of the concomitant drug.

See Table 1 for steps to prevent or manage these known or potentially significant drug interactions, including dosing recommendations [see section 4.3, CONTRAINDICATIONS and section 4.5, INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS].

PREVYMIS should be used with caution with drugs that are CYP3A substrates with narrow therapeutic ranges (e.g., alfentanil, fentanyl, and quinidine) as co-administration may result in increases in the plasma concentrations of CYP3A substrates. Close monitoring and/or dose adjustment of co-administered CYP3A substrates is recommended. [See Table 1 and section 4.5, INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS].

Use in hepatic impairment
No dose adjustment of PREVYMIS is required based on mild (Child-Pugh Class A) to moderate (Child-Pugh Class B) hepatic impairment. PREVYMIS is not recommended for patients with severe (Child-Pugh Class C) hepatic impairment [see section 4.2, DOSE AND METHOD OF ADMINISTRATION].

PREVYMIS is not recommended in patients with moderate hepatic impairment combined with moderate or severe renal impairment [see section 4.2, DOSE AND METHOD OF ADMINISTRATION].

Use in renal impairment
No dose adjustment of PREVYMIS is required based on renal impairment [see section 4.2, DOSE AND METHOD OF ADMINISTRATION]. There are no data in patients with end-stage renal disease (CrCl less than 10 mL/min), including patients on dialysis.

In patients with moderate or severe renal impairment (CrCl less than 50 mL/min) receiving PREVYMIS concentrated injection for infusion, accumulation of the intravenous vehicle, hydroxypropylbetadex, could occur. Serum creatinine levels should be closely monitored in these patients.

Use in the elderly

Safety and efficacy were similar across older and younger subjects in the Phase 3 trials in HSCT recipients and in the Phase 3 trial in kidney transplant recipients.

Paediatric use

Safety and efficacy of PREVYMIS in patients below 18 years of age have not been established.

Effects on laboratory tests

Overall, the percentage of subjects with potentially clinically significant changes in laboratory values (e.g., haematology, chemistry, renal, and hepatic function) was similar in the PREVYMIS and placebo groups. There were no differences in the incidence of or time to engraftment between the PREVYMIS and placebo groups.

Biomarkers of testicular toxicity were evaluated in male subjects in P001. The changes from baseline in male sex hormones (serum inhibin B, luteinising hormone (LH), follicle-stimulating hormone (FSH), and testosterone) were similar in the PREVYMIS and placebo groups.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effects of Other Drugs on PREVYMIS

Letermovir is a substrate of organic anion-transporting polypeptide 1B1/3 (OATP1B1/3) and P-glycoprotein (P-gp) transporters and UDP-glucuronosyltransferase 1A1/3 (UGT1A1/3) enzymes. Co-administration of PREVYMIS with drugs that are inhibitors of OATP1B1/3 transporters may result in increases in letermovir plasma concentrations. If PREVYMIS is co-administered with ciclosporin (a potent OATP1B1/3 inhibitor), the recommended dose of PREVYMIS is 240 mg once daily [see section 4.2, DOSE AND METHOD OF ADMINISTRATION].

Co-administration of PREVYMIS with strong and moderate inducers of transporters (e.g. P-gp) and/or enzymes (e.g. UGTs) is not recommended due to the potential for a decrease in letermovir plasma concentrations (see Table 1).

Rifampicin co-administration resulted in an initial increase in letermovir plasma concentrations (due to OAT1B1/3 inhibition) that is not clinically relevant, followed by clinically relevant decreases in letermovir plasma concentrations with continued rifampicin co-administration [see Table 7 in section 5.1 PHARMACODYNAMIC PROPERTIES, Drug Interaction Studies].

Effects of PREVYMIS on Other Drugs

Co-administration of PREVYMIS with midazolam results in increased midazolam plasma concentrations, indicating that letermovir is a moderate inhibitor of CYP3A. Co-administration of PREVYMIS with drugs that are CYP3A substrates may result in clinically

relevant increases in the plasma concentrations of co-administered CYP3A substrates [see section 4.3, CONTRAINDICATIONS, and section 4.4, SPECIAL WARNINGS AND PRECAUTIONS FOR USE] and Table 1.

Letermovir is an inhibitor of OATP1B1/3 transporters. Co-administration of PREVYMIS with drugs that are substrates of OATP1B1/3 transporters may result in a clinically relevant increase in plasma concentrations of co-administered OATP1B1/3 substrates (see Table 1).

Established and Other Potential Drug Interactions
If dose adjustments of concomitant medications are made due to treatment with PREVYMIS, doses should be readjusted after treatment with PREVYMIS is completed.

When PREVYMIS is co-administered with ciclosporin, the combined effect on CYP3A substrates may be similar to a strong CYP3A inhibitor. Refer to the prescribing information for dosing of the CYP3A substrate with a strong CYP3A inhibitor.

When PREVYMIS is co-administered with ciclosporin, the combined effect on agents that are both CYP3A and OATP1B1/3 substrates may be different than when they are administered with PREVYMIS alone. Refer to the prescribing information for both the co-administered drug and for ciclosporin.

Table 1 provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on studies conducted with PREVYMIS or are predicted drug interactions that may occur with PREVYMIS [see section 4.4, SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

Table 1: Potentially Significant Drug Interactions: Alteration in Dose May Be Recommended Based on Results from Drug Interaction Studies or Predicted Interactions*

Concomitant Drug Class and/or Clearance Pathway: Drug Name	**Effect on Concentration†**	**Clinical Comment**
Anti-arrhythmic Agents		
amiodarone	↑ amiodarone	Co-administration of PREVYMIS with amiodarone increases plasma concentrations of amiodarone. Close clinical monitoring for adverse events related to amiodarone is recommended during co-administration. Frequently monitor amiodarone concentrations.
Antibiotics		
nafcillin	↓ letermovir	Co-administration of PREVYMIS with nafcillin may decrease plasma concentrations of letermovir. Co-administration of PREVYMIS and nafcillin is not recommended.

Anticoagulants		
warfarin	↓ concentrations of warfarin	Co-administration of PREVYMIS with warfarin may decrease the plasma concentrations of warfarin. Frequent monitoring of INR should be performed while warfarin is co-administered with PREVYMIS[§].
Anticonvulsants		
carbamazepine	↓ letermovir	Co-administration of PREVYMIS with carbamazepine may decrease plasma concentrations of letermovir. Co-administration of PREVYMIS and carbamazepine is not recommended.
phenobarbital	↓ letermovir	Co-administration of PREVYMIS with phenobarbital may decrease plasma concentrations of letermovir. Co-administration of PREVYMIS and phenobarbital is not recommended.
phenytoin	↓ letermovir ↓ phenytoin	Co-administration of PREVYMIS with phenytoin may decrease plasma concentrations of letermovir. PREVYMIS may decrease the plasma concentrations of phenytoin. Co-administration of PREVYMIS and phenytoin is not recommended.
Antidiabetic agents		
glyburide	↑ glyburide	Co-administration of PREVYMIS with glyburide may increase the plasma concentration of glyburide. Frequent monitoring of glucose concentrations is recommended[§].
Antifungals		
voriconazole[‡]	↓ voriconazole	Co-administration of PREVYMIS with voriconazole decreases plasma concentrations of voriconazole. If concomitant administration is necessary, close monitoring for reduced effectiveness of voriconazole is recommended[§].
Antimycobacterials		
rifabutin	↓ letermovir	Co-administration of PREVYMIS with rifabutin may decrease plasma concentrations of letermovir. Co-administration of PREVYMIS and rifabutin is not recommended.

rifampicin‡	↓ letermovir	Co-administration of PREVYMIS with rifampicin decreases plasma concentrations of letermovir. Co-administration of PREVYMIS and rifampicin is not recommended.
Antipsychotics		
pimozide	↑ pimozide	Co-administration is contraindicated due to risk of QT prolongation and torsades de pointes [see section 4.3 CONTRAINDICATIONS].
thioridazine	↓ letermovir	Co-administration of PREVYMIS with thioridazine may decrease plasma concentrations of letermovir. Co-administration of PREVYMIS and thioridazine is not recommended.
Endothelin Antagonists		
bosentan	↓ letermovir	Co-administration of PREVYMIS with bosentan may decrease plasma concentrations of letermovir. Co-administration of PREVYMIS and bosentan is not recommended.
Ergot Alkaloids		
ergotamine dihydroergotamine	↑ ergotamine, dihydroergot-amine	Co-administration is contraindicated due to risk of ergotism [see section 4.3 CONTRAINDICATIONS].
Herbal Products		
St John's wort (*Hypericum perforatum*)	↓ letermovir	Co-administration of PREVYMIS with St. John's wort may decrease plasma concentrations of letermovir. Co-administration of PREVYMIS and St. John's wort is not recommended.
HIV Medications		
efavirenz	↓ letermovir	Co-administration of PREVYMIS with efavirenz may decrease plasma concentrations of letermovir. Co-administration of PREVYMIS and efavirenz is not recommended.
etravirine	↓ letermovir	Co-administration of PREVYMIS with etravirine may decrease plasma concentrations of letermovir. Co-administration of PREVYMIS and etravirine is not recommended.

nevirapine	↓ letermovir	Co-administration of PREVYMIS with nevirapine may decrease plasma concentrations of letermovir. Co-administration of PREVYMIS and nevirapine is not recommended.
HMG-CoA Reductase Inhibitors		
atorvastatin‡	↑ atorvastatin	Co-administration of PREVYMIS with atorvastatin increases plasma concentrations of atorvastatin. Statin-associated adverse events such as myopathy should be closely monitored. The dose of atorvastatin should not exceed 20 mg daily when co-administered with PREVYMIS§.
pitavastatin, simvastatin	↑ pitavastatin ↑ simvastatin	Co-administration of PREVYMIS and pitavastatin or simvastatin is not recommended. When PREVYMIS is co-administered with ciclosporin, use of either pitavastatin or simvastatin is contraindicated [see 4.3 CONTRAINDICATIONS].
Other HMG-CoA reductase inhibitors Examples: fluvastatin, lovastatin, pravastatin, rosuvastatin	↑ concentrations of HMG-CoA reductase inhibitors	PREVYMIS may increase statin plasma concentrations. Statin-associated adverse events such as myopathy should be closely monitored. A dose adjustment may be necessary when co-administered with PREVYMIS§.
Immunosuppressants		
ciclosporin‡	↑ ciclosporin ↑ letermovir	Co-administration of PREVYMIS with ciclosporin increases concentrations of both letermovir and ciclosporin. If PREVYMIS is co-administered with ciclosporin (a potent OATP1B1/3 inhibitor), the dosage of PREVYMIS should be decreased to 240 mg once daily [see 4.2 DOSE AND METHOD OF ADMINISTRATION]. Frequent monitoring of ciclosporin whole blood concentrations should be performed during and at discontinuation of PREVYMIS and the dose of ciclosporin adjusted accordingly§.
sirolimus‡	↑ sirolimus	Co-administration of PREVYMIS with sirolimus increases concentrations of sirolimus. Frequent monitoring of sirolimus whole blood concentrations should be performed during and at discontinuation of PREVYMIS and the dose of sirolimus adjusted accordingly§.

tacrolimus‡	↑ tacrolimus	Co-administration of PREVYMIS with tacrolimus increases tacrolimus plasma concentrations. Frequent monitoring of tacrolimus whole blood concentrations should be performed during and at discontinuation of PREVYMIS and the dose of tacrolimus adjusted accordingly§.
Proton pump inhibitors		
omeprazole, pantoprazole	↓ omeprazole ↓ pantoprazole	Co-administration of PREVYMIS with these proton pump inhibitors (PPI) may decrease plasma concentrations of the PPIs. Clinical monitoring and dose adjustment may be needed when co-administered with PREVYMIS§.
Wakefulness-Promoting Agents		
modafinil	↓ letermovir	Co-administration of PREVYMIS with modafinil may decrease plasma concentrations of letermovir. Co-administration of PREVYMIS and modafinil is not recommended.
CYP2C8 Substrates¶		
Examples: repaglinide rosiglitazone	↑ concentrations of CYP2C8 substrates	PREVYMIS may increase the plasma concentrations of CYP2C8 substrates. Frequent monitoring of glucose concentrations is recommended during co-administration of repaglinide or rosiglitazone§.
CYP3A Substrates		
Examples: alfentanil, fentanyl, midazolam‡, quinidine	↑ concentrations of CYP3A substrate	PREVYMIS increases or may increase the plasma concentrations of CYP3A substrates. When PREVYMIS is co-administered with a CYP3A substrate, refer to the prescribing information for dosing of the CYP3A substrate with a moderate CYP3A inhibitor§. Frequent monitoring for adverse reactions related to these agents is recommended during co-administration. Dose adjustment of CYP3A substrates may be needed§ [see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

* This table is not all inclusive.
† ↓ =decrease, ↑=increase
‡ These interactions have been studied.
§ Refer to the respective prescribing information.
¶ Based on physiologically based pharmacokinetic modelling.

Drugs without Clinically Significant Interactions with PREVYMIS
There was no clinically relevant interaction when PREVYMIS was co-administered with itraconazole, a P-gp/BCRP inhibitor (see Table 7 and Table 8).

There were no clinically relevant changes in plasma concentrations of digoxin, a P-gp substrate, and acyclovir, an OAT3 substrate, following co-administration with PREVYMIS in clinical studies.

The interaction between letermovir and the following drugs was evaluated in clinical studies: mycophenolate mofetil, fluconazole, posaconazole, and oral contraceptives (ethinylestradiol and levonorgestrel). No dose adjustments are needed when PREVYMIS is used with these drugs.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There were no effects on female fertility in rats. Impairment of fertility secondary to testicular toxicity was observed in male rats. Testicular toxicity in rats appears to be species-specific as this finding was not seen in male mice and monkeys, and the relevance to humans is unknown. In the Phase 3 trials in HSCT and kidney transplant recipients, there was no evidence of letermovir-related testicular toxicity [see section 4.8, ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

In the fertility and early embryonic development studies in the rat, there were no effects of letermovir on female fertility at the highest dose tested, 240 mg/kg/day (approximately 5-fold the AUC in humans at the recommended human dose (RHD)). In male rats, reduced sperm concentration, reduced sperm motility, and decreased fertility were observed at systemic exposures ≥ 3-fold the AUC in humans at the RHD. In male mice, there were no effects on testicular toxicity by histopathologic evaluation at systemic exposures approximately 4-fold the AUC in humans at the RHD.

In a study dedicated to investigate effects on the male reproductive system of mature monkeys administered letermovir, there was no evidence of testicular toxicity based on histopathologic evaluation, measurement of testicular size, blood hormone analysis (follicle stimulating hormone, inhibin B and testosterone) and sperm evaluation (sperm count, motility and morphology) at systemic exposures approximately 2-fold the AUC in humans at the RHD.

Use in pregnancy (Category B3)

No adequate human data are available to establish whether or not PREVYMIS poses a risk to pregnancy outcomes. Embryofetal toxicity was observed in rats and rabbits at maternally toxic systemic AUC exposures of approximately 11- and 2-fold, respectively, the AUC at the recommended human dose (RHD). For the purpose of calculating safety margins, the AUC at the RHD is defined as the mean AUC in HSCT recipients receiving 480 mg IV.

The background risk of major birth defects and miscarriage for the indicated population is unknown. The potential risk for humans is unknown. PREVYMIS should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Letermovir was administered orally to pregnant rats at 0, 10, 50 or 250 mg/kg/day from gestation days 6 to 17. Maternal toxicity (including decrease in body weight gain) was noted at 250 mg/kg/day (approximately 11-fold the AUC at the RHD); in the offspring, decreased fetal weight with delayed ossification, slightly oedematous fetuses, and increased incidence of shortened umbilical cords and of variations and malformations in the vertebrae, ribs, and pelvis were observed. No maternal or developmental effects were noted at the dose of 50 mg/kg/day (approximately 2.5-fold the AUC at the RHD).

Letermovir was administered orally to pregnant rabbits at 0, 25, 75 or 225 mg/kg/day from gestation days 6 to 20. Maternal toxicity (including mortality and abortions) was noted at 225 mg/kg/day (approximately 2-fold the AUC at the RHD); in the offspring, an increased incidence of malformations and variations in the vertebrae and ribs were observed. No maternal or developmental effects were noted at the dose of 75 mg/kg/day (at less than the AUC at the RHD).

In the pre- and post-natal developmental study, letermovir was administered orally to pregnant rats at 0, 10, 45 or 180 mg/kg/day from gestation day 6 to lactation day 22. There were increased number of dams with total litter loss and slight delays in postnatal development (reduced body weight gain and delayed vaginal opening) observed at the highest exposure tested (2-fold the AUC at the RHD).

Use in lactation

It is not known whether letermovir is present in human breast milk, affects human milk production, or has effects on the breastfed child.

When administered to lactating rats, letermovir was present in milk, without effects on growth and development in nursing pups.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PREVYMIS and any potential adverse effects on the breastfed child from PREVYMIS or from the underlying maternal condition.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

PREVYMIS is not likely to have an effect on the ability to drive or use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

Adults

Adult CMV-seropositive Recipients [R+] of an Allogeneic HSCT

Prophylaxis Through Week 14 (~100 days) Post-HSCT

The safety of PREVYMIS was evaluated in a Phase 3 randomised, double-blind, placebo-controlled trial (P001) in which 565 subjects were randomised and treated with PREVYMIS (N=373) or placebo (N=192) through Week 14 post-HSCT. Adverse events were those reported while subjects were on study medication or within two weeks of study medication completion/discontinuation. The mean time for reporting adverse events and laboratory abnormalities was approximately 22% longer in the PREVYMIS arm compared to the placebo arm.

Cardiac Adverse Events

The cardiac adverse event rate (regardless of investigator causality) was higher in subjects receiving PREVYMIS (13%) compared to subjects receiving placebo (6%). The most common cardiac adverse events were tachycardia (reported in 4% of PREVYMIS subjects and in 2% of placebo subjects) and atrial fibrillation (reported in 3% of PREVYMIS subjects and in 1% of placebo subjects). Among those subjects who experienced one or more cardiac adverse events, 85% of PREVYMIS and 92% of placebo subjects had events reported as mild or moderate in severity.

Common Adverse Events
The rate of adverse events occurring in at least 10% of subjects in the PREVYMIS group and at a frequency at least 2% greater than placebo are outlined in Table 2.

Table 2: Trial P001 All Grade Adverse Events Reported in ≥10% of PREVYMIS-Treated HSCT Recipients at a Frequency at least 2% Greater than Placebo

Adverse Events	PREVYMIS (N=373)	Placebo (N=192)
nausea	27%	23%
diarrhoea	26%	24%
vomiting	19%	14%
peripheral oedema	14%	9%
cough	14%	10%
headache	14%	9%
fatigue	13%	11%
abdominal pain	12%	9%

Overall, similar proportions of subjects in each group discontinued study medication due to an adverse event (13% of PREVYMIS subjects vs. 12% of placebo subjects). The most frequently reported adverse event that led to study drug discontinuation was nausea, occurring in 2% of PREVYMIS subjects and 1% of placebo subjects. Hypersensitivity reaction, with associated moderate dyspnoea, occurred in one subject following the first infusion of IV PREVYMIS after switching from oral PREVYMIS, leading to treatment discontinuation.

Laboratory Abnormalities
Selected laboratory abnormalities reported during treatment or within 2 weeks of stopping treatment are presented in the table below.

Table 3: Trial P001 Selected Laboratory Abnormalities

	PREVYMIS N=373	Placebo N=192
Absolute neutrophil count (cells/µL)		
< 500	19%	19%
500 – < 750	4%	7%
750 – < 1000	8%	9%
Hemoglobin (g/dL)		
< 6.5	2%	1%
6.5 – < 8.0	14%	15%
8.0 – < 9.5	41%	43%
Platelets (cells/µL)		
< 25000	27%	21%
25000 – < 50000	17%	18%
50000 – < 100000	20%	30%
Serum creatinine (mg/dL)		
> 2.5	2%	3%
> 1.5 – 2.5	17%	20%

The median time to engraftment (defined as absolute neutrophil count ≥500/mm^3 on 3 consecutive days after transplantation) was 19 days in the PREVYMIS group and 18 days in the placebo group.

Prophylaxis From Week 14 (~100 days) Through Week 28 (~200 days) Post-HSCT
The safety of PREVYMIS was evaluated in a Phase 3 randomised, double-blind, placebo-controlled trial (P040) in which 218 subjects who completed PREVYMIS prophylaxis through ~100 days post-HSCT were randomised to treatment with PREVYMIS (N=144) or placebo (N=74) through Week 28 (~200 days) post-HSCT and were followed for safety through Week 48 post-HSCT. Adverse events were those reported while subjects were on study drug or within two weeks of study drug completion/discontinuation.

Adverse events reported in at least 10% of subjects in the PREVYMIS group included diarrhoea (PREVYMIS, 12%; placebo, 12%) and nausea (PREVYMIS, 11%; placebo, 18%). Study drug was discontinued due to an adverse event in 5% of PREVYMIS subjects and 1% of placebo subjects. None of the adverse events leading to discontinuation of study drug was considered to be drug-related. The cardiac adverse event rate (regardless of investigator-assessed causality) was 4% in the PREVYMIS and placebo groups; no cardiac adverse event was reported more than once in either group.

Adult Kidney Transplant Recipients [D+/R-]
The safety of PREVYMIS was evaluated in a Phase 3 randomized, double-blind, active comparator controlled trial (P002) in which 589 subjects were treated with PREVYMIS (N=292) or valganciclovir (N=297) through Week 28 post-transplant. Adverse events were those reported while subjects were on study medication or within two weeks of study medication completion/discontinuation.

There was one adverse event, diarrhoea, reported in at least 10% of subjects in the PREVYMIS group and at a frequency greater than valganciclovir (PREVYMIS, 32%; valganciclovir, 29%). Study drug was discontinued due to an adverse event in 4% of PREVYMIS subjects and 14% of valganciclovir subjects. The most frequently reported adverse events that led to study drug discontinuation were neutropenia (PREVYMIS, 1%; valganciclovir, 2%) and leukopenia (PREVYMIS, 1%; valganciclovir, 5%).

The proportion of subjects with leukopenia or neutropenia (adverse events of leukopenia or neutropenia, total white blood cell count <3500 cells/µL, or absolute neutrophil count <1000 cells/µL) through Week 28 post-transplant was lower in the PREVYMIS group compared with the valganciclovir group (PREVYMIS, 26%; valganciclovir, 64%).

Post-Marketing Experience
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 http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

There is limited experience with human overdosage with PREVYMIS. During Phase 1 clinical trials, 86 healthy subjects received doses ranging from 720 mg/day to 1440 mg/day of PREVYMIS for up to 14 days. The adverse reaction profile was similar to that of the clinical

dose of 480 mg/day. There is no specific antidote for overdose with PREVYMIS. In case of overdose, it is recommended that the patient be monitored for adverse reactions and appropriate symptomatic treatment instituted.

It is unknown whether dialysis will result in meaningful removal of PREVYMIS from systemic circulation.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Letermovir inhibits the CMV DNA terminase complex, which is required for viral replication. Biochemical characterisation and electron microscopy demonstrated that letermovir affects the formation of proper unit length genomes and interferes with virion maturation.

Clinical trials

Adult CMV-seropositive Recipients [R+] of an Allogeneic Haematopoietic Stem Cell Transplant

Prophylaxis Through Week 14 (~100 days) Post-HSCT

To evaluate PREVYMIS prophylaxis as a preventive strategy for CMV infection or disease in transplant recipients at high risk for CMV reactivation, the efficacy of PREVYMIS was assessed in a multicenter, double-blind, placebo-controlled Phase 3 trial (P001) in adult CMV-seropositive recipients [R+] of an allogeneic HSCT. Subjects were randomised (2:1) to receive either PREVYMIS at a dose of 480 mg once daily adjusted to 240 mg when co-administered with ciclosporin, or placebo. Randomisation was stratified by investigational site and risk level (high vs. low strata) for CMV reactivation at the time of study entry. Study drug was initiated after HSCT (Day 0-28 post-HSCT) and continued through Week 14 post-HSCT. Study drug was administered either orally or IV; the dose of PREVYMIS was the same regardless of the route of administration. Subjects were monitored through Week 24 post-HSCT for the primary efficacy endpoint with continued follow-up through Week 48 post-HSCT.

Among the 565 treated subjects, 373 subjects received PREVYMIS (including 99 subjects who received at least one IV dose) and 192 received placebo (including 48 subjects who received at least one IV dose). The median time to starting study drug was 9 days after transplantation. Thirty-seven percent (37%) of subjects were engrafted at baseline. The median age was 54 years (range: 18 to 78 years); 58% were male; 82% were White; 10% were Asian; 2% were Black or African; and 7% were Hispanic or Latino. At baseline, 50% of subjects received a myeloablative regimen, 52% were receiving ciclosporin, and 42% were receiving tacrolimus. The most common primary reasons for transplant were acute myeloid leukemia (38%), myeloblastic syndrome (15%), and lymphoma (13%). Twelve percent (12%) of subjects were positive for CMV DNA at baseline, and were therefore excluded from the primary efficacy analysis.

At baseline, 31% of subjects were in the high risk stratum as defined by one or more of the following criteria: Human Leukocyte Antigen (HLA)-related (sibling) donor with at least one mismatch at one of the following three HLA-gene loci: HLA-A, -B or –DR, haploidentical donor; unrelated donor with at least one mismatch at one of the following four HLA-gene loci: HLA-A, -B, -C and -DRB1; use of umbilical cord blood as stem cell source; use of *ex vivo* T-cell-depleted grafts; Grade 2 or greater Graft-Versus-Host Disease (GVHD), requiring systemic corticosteroids. The remaining 69% of subjects did not meet any of these high risk stratum criteria and were therefore included in the low risk stratum.

Efficacy

Clinically Significant CMV Infection

The primary efficacy endpoint of P001 was the incidence of clinically significant CMV infection through Week 24 post-HSCT. Clinically significant CMV infection was defined as the occurrence of either CMV end-organ disease, or initiation of anti-CMV pre-emptive therapy (PET) based on documented CMV viraemia (using the Roche COBAS® AmpliPrep/COBAS TaqMan® assay, LLoQ is 137 IU/mL, which is approximately 150 copies/mL) and the clinical condition of the subject. The Non-Completer=Failure (NC=F) approach was used, where subjects who discontinued from the study prior to Week 24 post-HSCT or had a missing outcome at Week 24 post-HSCT were counted as failures.

PREVYMIS demonstrated superior efficacy over placebo in the analysis of the primary endpoint, as shown in Table 4. The estimated treatment difference of -23.5% was statistically significant (one-sided p value <0.0001).

Table 4: P001 Efficacy Results in HSCT Recipients (NC=F Approach, FAS Population)

Parameter	**PREVYMIS (N=325) n (%)**	**Placebo (N=170) n (%)**
Primary Endpoint (Proportion of subjects who failed prophylaxis)	**122 (37.5)**	**103 (60.6)**
Reasons for Failures*		
Clinically significant CMV infection by Week 24†	57 (17.5)	71 (41.8)
Initiation of PET based on documented CMV viraemia	52 (16.0)	68 (40.0)
CMV end-organ disease	5 (1.5)	3 (1.8)
Discontinued from study before Week 24	56 (17.2)	27 (15.9)
Missing outcome in Week 24 visit window	9 (2.8)	5 (2.9)
Stratum-adjusted treatment difference (PREVYMIS-Placebo)‡		
Difference (95% CI)	-23.5 (-32.5, -14.6)	
p-value	<0.0001	

* The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.

† Clinically significant CMV infection was defined as CMV end organ disease or initiation of PET based on documented CMV viraemia and the clinical condition of the subject.

‡ 95% CIs and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A 1-sided p-value ≤0.0249 was used for declaring statistical significance.

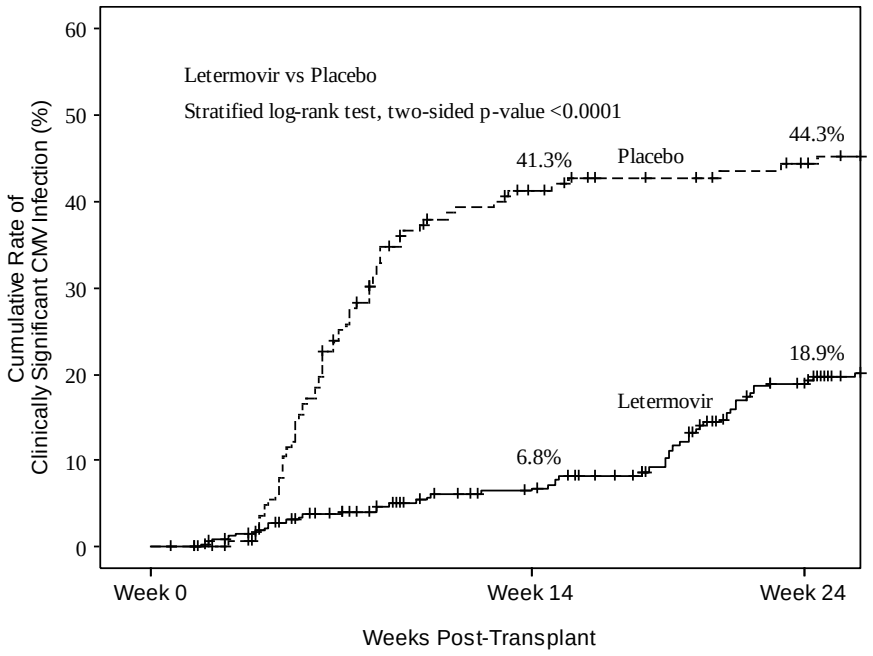
Note: FAS=Full analysis set; FAS includes randomised subjects who received at least one dose of study medication, and excludes subjects with detectable CMV DNA at baseline. Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all subjects who developed clinically significant CMV infection or

prematurely discontinued from the study or had a missing outcome through Week 24 post-HSCT visit window.
N = number of subjects in each treatment group.
n (%) = Number (percent) of subjects in each sub-category.
Note: Among the 70 subjects with CMV viraemia on Day 1 (who were excluded from the FAS population), the proportion that developed clinically significant CMV infection in the letermovir group was 64.6% (31/48) compared to 90.9% (20/22) in the placebo group through Week 24 post-HSCT. The estimated difference (95% CI for the difference) was -26.1% (-45.9%, -6.3%), with a nominal one-sided p-value <0.0048.

At Week 24 post-HSCT, the Kaplan-Meier (K-M) event rate for clinically significant CMV infection was 18.9% in the PREVYMIS group compared to 44.3% in the placebo group (nominal two-sided stratified log-rank p-value<0.0001) (see Figure 1). Factors associated with clinically significant CMV infection between Week 14 and Week 24 post-HSCT among PREVYMIS-treated subjects included high risk for CMV reactivation at baseline, having GVHD, and steroid use at any time after randomisation.

Of the 373 subjects treated with PREVYMIS in P001, 56 (15.0%) subjects were 65 years of age or older. Safety and efficacy were similar across older and younger subjects.

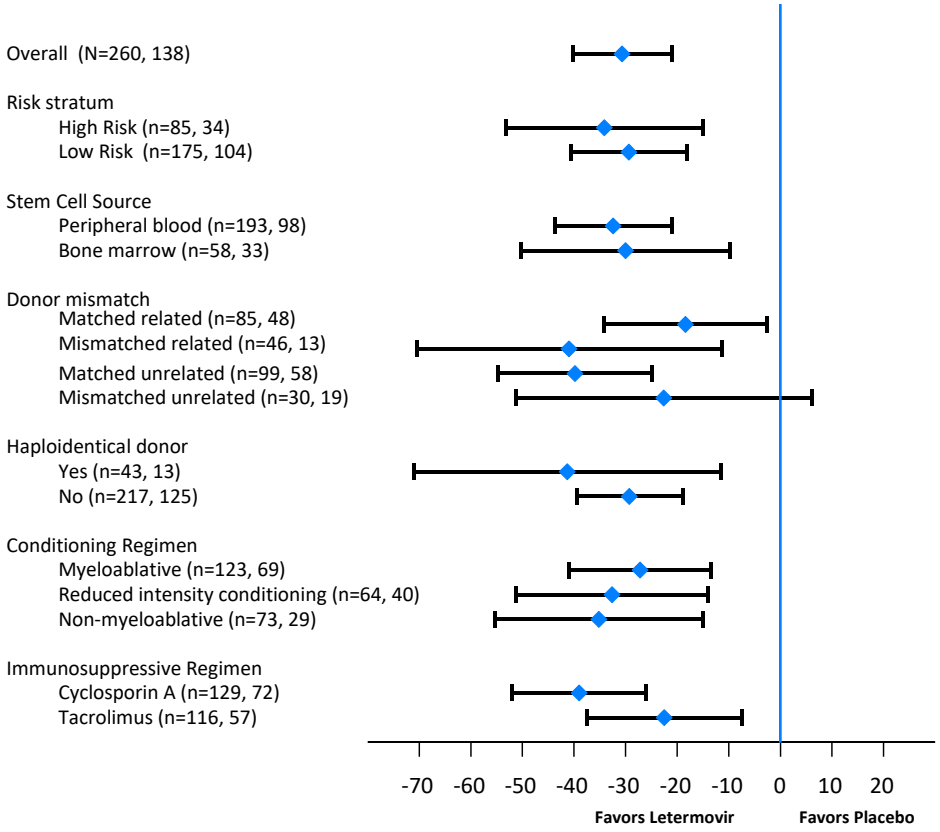
Figure 1: P001: Kaplan-Meier Plot of Time to Onset of Clinically Significant CMV Infection Through Week 24 Post-Transplant in HSCT Recipients (FAS Population)



Number of Subjects at Risk			
Letermovir	325	270	212
Placebo	170	85	70

Efficacy consistently favoured PREVYMIS across subgroups including low and high risk strata for CMV reactivation, conditioning regimens, and concomitant immunosuppressive regimens.

Figure 2: P001 Forest Plot of the Proportion of Subjects with Clinically Significant CMV Infection Through Week 24 Post-HSCT by Selected Subgroups (DAO Approach, FAS Population)

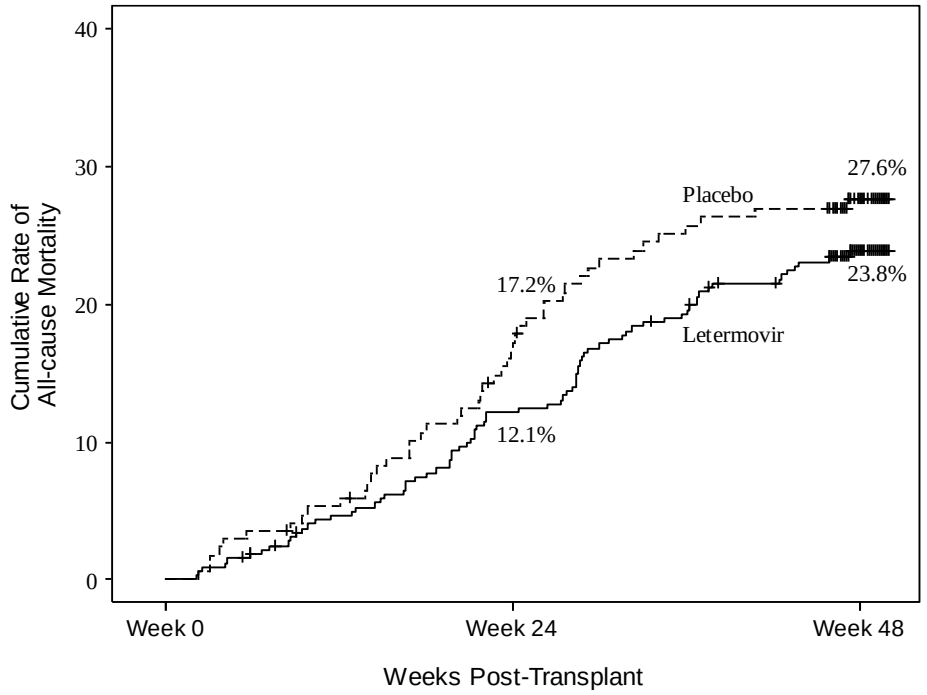


DAO= data as observed. With DAO approach, any subject with a missing value was excluded from the analysis.

Mortality

The K-M event rate for all-cause mortality in the letermovir vs. placebo groups was 12.1% vs. 17.2% at Week 24 post-HSCT (nominal two-sided stratified log-rank p-value=0.0401), and 23.8% vs. 27.6% at Week 48 post-HSCT (nominal two-sided stratified log-rank p-value=0.2117; see Figure 3).

Figure 3: P001: Kaplan-Meier Plot of Time to All-Cause Mortality Through Week 48 Post-Transplant in HSCT Recipients (FAS Population)



Number of Subjects at Risk			
Letermovir	325	282	165
Placebo	170	139	81

Prophylaxis From Week 14 (~100 days) Through Week 28 (~200 days) Post-HSCT

The efficacy of extending PREVYMIS prophylaxis from Week 14 (~100 days) through Week 28 (~200 days) post-HSCT in patients at risk for late CMV infection and disease was assessed in a multicenter, double-blind, placebo-controlled Phase 3 trial (P040) in adult CMV-seropositive recipients [R+] of an allogeneic HSCT. Eligible subjects who completed PREVYMIS prophylaxis through ~100 days post-HSCT were randomised (2:1) to receive PREVYMIS or placebo from Week 14 through Week 28 post-HSCT. Subjects received PREVYMIS at a dose of 480 mg once daily (adjusted to 240 mg when co-administered with cyclosporine) or placebo. Study drug was administered either orally or IV; the dose of PREVYMIS was the same regardless of the route of administration. Subjects were monitored through Week 28 post-HSCT for the primary efficacy endpoint with continued off-treatment follow-up through Week 48 post-HSCT.

Among the 218 treated subjects, 144 subjects received PREVYMIS and 74 received placebo. The median age was 55 years (range: 20 to 74 years); 62% were male; 79% were white; 11% were Asian; 2% were Black; and 10% were Hispanic or Latino. The most common reasons for transplant were acute myeloid leukemia (42%), acute lymphocytic leukemia (15%), and myelodysplastic syndrome (11%).

At study entry, all subjects had risk factors for late CMV infection and disease, with 64% having two or more risk factors. The risk factors included: HLA-related (sibling) donor with at least one mismatch at one of the following three HLA-gene loci: HLA-A, -B or –DR; haploidentical donor; unrelated donor with at least one mismatch at one of the following four HLA-gene loci: HLA-A, -B, -C and -DRB1; use of umbilical cord blood as stem cell source; use of *ex vivo* T-cell-depleted grafts; receipt of anti-thymocyte globulin; receipt of alemtuzumab; use of systemic prednisone (or equivalent) at a dose of ≥1 mg/kg of body weight per day.

Efficacy

Clinically Significant CMV Infection

The primary efficacy endpoint of P040 was the incidence of clinically significant CMV infection through Week 28 post-HSCT. Clinically significant CMV infection was defined as the occurrence of either CMV end-organ disease, or initiation of anti-CMV PET based on documented CMV viraemia and the clinical condition of the subject. The Observed Failure (OF) approach was used, where subjects who developed clinically significant CMV infection or discontinued prematurely from the study with viraemia were counted as failures.

PREVYMIS demonstrated statistically superior efficacy over placebo in the analysis of the primary endpoint, as shown in Table 5. The estimated treatment difference of -16.1% was statistically significant (one-sided p-value=0.0005).

Table 5: P040 Efficacy Results in HSCT Recipients at Risk for Late CMV Infection and Disease (OF Approach, FAS Population)

Parameter	PREVYMIS (~200 days PREVYMIS) (N=144) n (%)	Placebo (~100 days PREVYMIS) (N=74) n (%)
Failures*	**4 (2.8)**	**14 (18.9)**
Clinically significant CMV infection through Week 28†	2 (1.4)	13 (17.6)
Initiation of PET based on documented CMV viraemia	1 (0.7)	11 (14.9)
CMV end-organ disease	1 (0.7)	2 (2.7)
Discontinued from study with CMV viraemia before Week 28	2 (1.4)	1 (1.4)
Stratum-adjusted treatment difference (PREVYMIS (~200 days PREVYMIS)-Placebo (~100 days PREVYMIS))‡		
Difference (95% CI)	-16.1 (-25.8, -6.5)	
p-value	0.0005	

* The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.

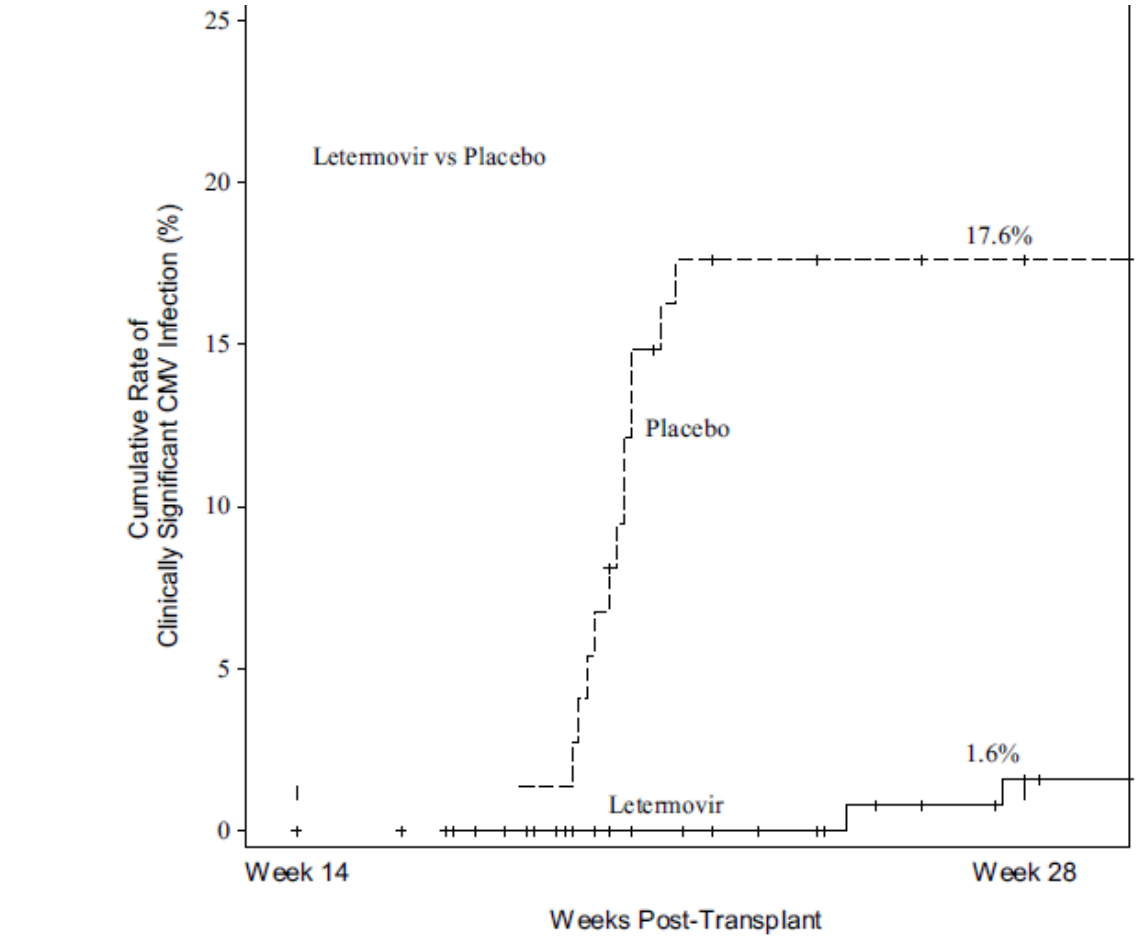
† Clinically significant CMV infection was defined as CMV end-organ disease (proven or probable) or initiation of PET based on documented CMV viraemia and the clinical condition of the subject.

‡ 95% CIs and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (haploidentical donor yes or no). A one-sided p-value ≤0.0249 was used for declaring statistical significance.

Approach to handling missing values: Observed Failure (OF) approach. With the OF approach, failure was defined as all subjects who developed clinically significant CMV infection or discontinued prematurely from the study with CMV viraemia from Week 14 (~100 days) through Week 28 (~200 days) post-HSCT.
N = Number of subjects in each treatment group.
n (%) = Number (percent) of subjects in each sub-category.

The time to onset of clinically significant CMV infection was substantially longer in PREVYMIS-treated subjects compared with placebo-treated subjects when PREVYMIS prophylaxis was extended from ~100 days to ~200 days post-HSCT (see Figure 4).

Figure 4: P040 Kaplan-Meier Plot of Time to Onset of Clinically Significant CMV Infection From Week 14 (~100 days) Through Week 28 (~200 days) Post-transplant in HSCT Recipients at Risk for Late CMV Infection and Disease (FAS Population)



Number of Subjects at Risk		
Letermovir	143	123
Placebo	74	60

Adult CMV-seronegative Recipients of a Kidney Transplant from a CMV-seropositive Donor [D+/R-]

To evaluate PREVYMIS prophylaxis as a preventive strategy for CMV disease in kidney transplant recipients, the efficacy of PREVYMIS was assessed in a multicenter, double-blind, active comparator-controlled Phase 3 trial (P002) in adult kidney transplant recipients at high risk [D+/R-]. Subjects were randomised (1:1) to receive either PREVYMIS or valganciclovir (900mg). PREVYMIS was administered at a dose of 480 mg once daily (adjusted to 240 mg when co-administered with cyclosporine). Randomization was stratified by the use or nonuse of highly cytolytic, anti-lymphocyte immunotherapy during induction. Study drug was initiated between Day 0 and Day 7 post-kidney transplant and continued through Week 28 (~200 days) post-transplant. Study drug was administered either orally or IV; a similar dose of PREVYMIS was administered IV. Subjects were monitored through Week 52 post-transplant.

Among the 589 treated subjects, 292 subjects received PREVYMIS and 297 received valganciclovir. The median age was 51 years (range: 18 to 82 years); 72% were male; 84% were White; 2% were Asian; 9% were Black; 17% were Hispanic or Latino; and 60% received a kidney from a deceased donor. The most common primary reasons for transplant were congenital cystic kidney disease (17%), hypertension (16%), and diabetes/diabetic nephropathy (14%).

Efficacy

CMV Disease

The primary efficacy endpoint of P002 was the incidence of CMV disease (CMV end-organ disease or CMV syndrome, confirmed by an independent adjudication committee) through Week 52 post-transplant. The Observed Failure (OF) approach was used, where subjects who discontinued prematurely from the study for any reason or were missing data at the timepoint were not considered failures.

PREVYMIS demonstrated non-inferiority to valganciclovir in the analysis of the primary endpoint, as shown in Table 6.

Table 6: P002 Efficacy Results in Kidney Transplant Recipients (OF Approach, FAS Population)

Parameter	PREVYMIS (N=289) n (%)	Valganciclovir (N=297) n (%)
CMV disease* through Week 52	**30 (10.4)**	**35 (11.8)**
Stratum-adjusted treatment difference (PREVYMIS-Valganciclovir)† Difference (95% CI)	-1.4 (-6.5, 3.8)‡	
* CMV disease cases confirmed by an independent adjudication committee. † The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (use/nonuse of highly cytolytic, anti-lymphocyte immunotherapy during induction). ‡ Based on a non-inferiority margin of 10%, PREVYMIS is non-inferior to valganciclovir.		

Approach to handling missing values: Observed Failure (OF) approach. With OF approach, subjects who discontinue prematurely from the study for any reason are not considered failures.
Note: Subjects randomised to the PREVYMIS group were given acyclovir for herpes simplex virus (HSV) and varicella zoster virus (VZV) prophylaxis. Subjects randomised to the valganciclovir group were given a placebo to acyclovir.
N = number of subjects in each treatment group.
n (%) = Number (percent) of subjects in each sub-category.

No subjects in the PREVYMIS group experienced CMV disease through Week 28 post-transplant compared with 5 subjects in the valganciclovir group.

Pharmacodynamics

Cardiac Electrophysiology

The effect of letermovir on doses up to 960 mg given IV on the QTc interval was evaluated in a randomised, single-dose, placebo- and active-controlled (moxifloxacin 400 mg oral) 4-period crossover thorough QT trial in 38 healthy subjects. Letermovir does not prolong QTc to any clinically relevant extent following the 960 mg IV dose, with plasma concentrations approximately 2-fold higher than the 480 mg IV dose.

Microbiology

Antiviral Activity

The median EC_{50} value of letermovir against a collection of clinical CMV isolates in a cell-culture model of infection was 2.1 nM (range = 0.7 nM to 6.1 nM, n=74).

Viral Resistance

In Cell Culture

The CMV genes UL51, UL56, and UL89 encode subunits of CMV DNA terminase. CMV mutants with reduced susceptibility to letermovir have been selected in cell culture, and the substitutions map to pUL51 (P91S, A95V), pUL56 (C25F, S229F, V231A, V231L, N232Y, V236A, V236L, V236M, E237D, L241P, T244K, T244R, L254F, L257F, L257I, K258E, F261C, F261L, F261S, Y321C, C325F, C325R, C325W, C325Y, L328V, M329T, A365S, N368D, R369G, R369M, R369S), and pUL89 (N320H, D344E). EC_{50} values for recombinant CMV mutants expressing these substitutions are 1.6- to 9,300-fold higher than those for the wild-type reference virus.

In Clinical Studies

In a Phase 2b trial evaluating letermovir doses of 60, 120, or 240 mg/day or placebo for up to 84 days in 131 HSCT recipients, DNA sequence analysis of a select region of UL56 (amino acids 231 to 369) was performed on samples obtained from 12 letermovir-treated subjects who experienced prophylaxis failure and for whom samples were available for analysis. One subject (who received 60 mg/day) had a letermovir resistant genotypic variant (GV) (V236M).

In a Phase 3 trial (P001), DNA sequence analysis of the entire coding regions of UL56 and UL89 was performed on samples obtained from 40 letermovir-treated subjects in the FAS population who experienced prophylaxis failure and for whom samples were available for analysis. A total of 2 letermovir resistance-associated substitutions both mapping to pUL56 were detected in 2 subjects. One subject had the substitution V236M, and the other had E237G.

Cross Resistance

Cross resistance is not likely with drugs outside of this class. Letermovir is fully active against viral populations with substitutions conferring resistance to CMV DNA polymerase inhibitors (ganciclovir, cidofovir, and foscarnet). A panel of recombinant CMV strains with substitutions conferring resistance to letermovir was fully susceptible to cidofovir, foscarnet and ganciclovir with the exception of a recombinant strain with the pUL56 E237G substitution which confers a 2.1-fold reduction in ganciclovir susceptibility relative to wild-type.

Pharmacogenomics

The impact of genetic variants in the OATP1B1 gene SLCO1B1 (rs4149056, rs2306283, rs4149032) and UGT1A1 (rs4148323 and the promoter TA repeat variants) on the pharmacokinetics of letermovir was evaluated in 299 study participants. There was no clinically relevant impact of these variants on letermovir exposure

Drug Interaction Studies

Drug interaction studies were performed in healthy subjects with PREVYMIS and drugs likely to be co-administered or drugs commonly used as probes for pharmacokinetic interactions (see Table 7 and Table 8).

In vitro results indicate that letermovir is a substrate of OATP1B1/3, P-gp, UGT1A1, and UGT1A3. Inhibitors of OATP1B1/3 transporters may result in increases in letermovir plasma concentrations. If PREVYMIS is co-administered with ciclosporin (a potent OATP1B1/3 inhibitor), the recommended dose of PREVYMIS is 240 mg once daily [see section 4.2, DOSE AND METHOD OF ADMINISTRATION]. Changes in letermovir plasma concentrations due to inhibition of P-gp/BCRP by itraconazole were not clinically relevant. Inhibition of UGTs is not anticipated to have a clinically relevant effect on letermovir plasma concentrations. Induction of drug enzymes (e.g. UGTs) and/or transporters (e.g. P-gp) by rifampicin may result in clinically relevant decreases in letermovir plasma concentrations; therefore, co-administration of strong and moderate inducers with letermovir is not recommended [see section 4.5, INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, Effects of Other Drugs of PREVYMIS], Table 1 and Table 7. Although CYP3A, CYP2D6 and CYP2J2 were identified as enzymes capable of mediating the metabolism of letermovir *in vitro*, oxidative metabolism is considered to be a minor elimination pathway based on *in vivo* human data. Likewise, letermovir was found to be a substrate of BSEP *in vitro*; the clinical relevance is unknown.

Letermovir is a time-dependent inhibitor and inducer of CYP3A *in vitro*. Co-administration of PREVYMIS with midazolam resulted in increased exposure of midazolam, indicating that the net effect of letermovir on CYP3A is moderate inhibition (see Table 8). Based on these results, co-administration of PREVYMIS with CYP3A substrates may increase the plasma concentrations of the CYP3A substrates [see section 4.3, CONTRAINDICATIONS, section 4.4, SPECIAL WARNINGS AND PRECAUTIONS FOR USE, and section 4.5, INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS] and Table 1. Letermovir is a reversible inhibitor of CYP2C8 *in vitro*. Physiologically based pharmacokinetic modeling predicts an increase in plasma concentrations of CYP2C8 substrates when co-administered with PREVYMIS [see Table 1].

Co-administration of PREVYMIS reduced the exposure of voriconazole, most likely due to the induction of voriconazole elimination pathways, CYP2C9 and CYP2C19. Co-administration of PREVYMIS with CYP2C9 and CYP2C19 substrates may decrease the plasma concentrations of the CYP2C9 and CYP2C19 substrates [see Table 1]. Letermovir is an inducer of CYP2B6 *in vitro*; the clinical relevance is unknown.

Letermovir inhibited efflux transporters P-gp, breast cancer resistance protein (BCRP), bile salt export pump (BSEP), multidrug resistance-associated protein 2 (MRP2), OAT3, and hepatic uptake transporter OATP1B1/3 *in vitro*. Co-administration of PREVYMIS with substrates of OATP1B1/3 transporters (e.g., atorvastatin, a known substrate of CYP3A, OATP1B1/3, and potentially BCRP) may result in a clinically relevant increase in plasma concentrations of OATP1B1/3 substrates [see Table 1]. There were no clinically relevant changes in plasma concentrations of digoxin, a P-gp substrate, or acyclovir, an OAT3 substrate, following co-administration with PREVYMIS in clinical studies (see Table 8). The effect of letermovir on BCRP, BSEP, and MRP2 substrates was not evaluated in clinical studies; the clinical relevance is unknown.

Table 7: Drug Interactions: Changes in Pharmacokinetics of Letermovir in the Presence of Co-administered Drug

Co-administered Drug	Regimen of Co-administered Drug	Letermovir Regimen	N	Geometric Mean Ratio [90% CI] of Letermovir PK with/without Co-administered Drug (No Effect=1.00)	
				AUC	Cmax
Antifungal Agents					
fluconazole	400 mg single dose PO	480 mg single dose PO	14	1.11 (1.01, 1.23)	1.06 (0.93, 1.21)
itraconazole	200 mg once daily PO	480 mg once daily PO	14	1.33 (1.17, 1.51)	1.21 (1.05, 1.39)
Antimycobacterials					
rifampicin	600 mg single dose PO	480 mg single dose PO	16	2.03 (1.84, 2.26)	1.59 (1.46, 1.74)
	600 mg single dose IV	480 mg single dose PO	16	1.58 (1.38, 1.81)	1.37 (1.16, 1.61)
	600 mg once daily PO*	480 mg once daily PO	14	0.81 (0.67, 0.98)	1.01 (0.79, 1.38)
	600 mg once daily PO (24 hours after rifampicin)†	480 mg once daily PO	14	0.15 (0.13, 0.17)	0.27 (0.22, 0.31)
Immunosupressants					
ciclosporin	200 mg single dose PO	240 mg once daily PO	12	2.11 (1.97, 2.26)	1.48 (1.33, 1.65)

Co-administered Drug	Regimen of Co-administered Drug	Letermovir Regimen	N	Geometric Mean Ratio [90% CI] of Letermovir PK with/without Co-administered Drug (No Effect=1.00)	
				AUC	Cmax
mycophenolate mofetil	1 g single dose PO	480 mg once daily PO	14	1.18 (1.04, 1.32)	1.11 (0.92, 1.34)
tacrolimus	5 mg single dose PO	80 mg twice daily PO	14	1.02 (0.97, 1.07)	0.92 (0.84, 1.00)
Abbreviations: PO= oral *C24 GMR [90%] is 0.14 (0.11, 0.19) † These data are the effect of rifampicin on letermovir 24 hours after the final rifampicin dose. C24 GMR [90%] is 0.09 (0.06, 0.12).					

Table 8: Drug Interactions: Changes in Pharmacokinetics for Co-administered Drug in the Presence of Letermovir or Co-administered Letermovir

Co-administered Drug	Regimen of Co-administered Drug	Letermovir Regimen	N	Geometric Mean Ratio [90% CI] of Co-administered Drug PK with/without Letermovir (No Effect=1.00)	
				AUC	Cmax
CYP3A Substrates					
midazolam	1 mg single dose IV	240 mg once daily PO	16	1.47 (1.37, 1.58)	1.05 (0.94, 1.17)
	2 mg single dose PO	240 mg once daily PO	16	2.25 (2.04, 2.48)	1.72 (1.55, 1.92)
P-gp Substrates					
digoxin	0.5 mg single dose PO	240 mg twice daily PO	22	0.88 (0.80, 0.96)	0.75 (0.63, 0.89)
Immunosuppressants					
ciclosporin	50 mg single dose PO	240 mg once daily PO	14	1.66 (1.51, 1.82)	1.08 (0.97, 1.19)
mycophenolate mofetil	1 g single dose PO	480 mg once daily PO	14	1.08 (0.97, 1.20)	0.96 (0.82, 1.12)
tacrolimus	5 mg single dose PO	480 mg once daily PO	13	2.42 (2.04, 2.88)	1.57 (1.32, 1.86)
sirolimus	2 mg single dose PO	480 mg once daily PO	13	3.40 (3.01, 3.85)	2.76 (2.48, 3.06)
Antifungal and Antiviral Agents					

Co-administered Drug	Regimen of Co-administered Drug	Letermovir Regimen	N	Geometric Mean Ratio [90% CI] of Co-administered Drug PK with/without Letermovir (No Effect=1.00)	
				AUC	Cmax
acyclovir	400 mg single dose PO	480 mg once daily PO	13	1.02 (0.87, 1.2)	0.82 (0.71, 0.93)
fluconazole	400 mg single dose PO	480 mg single dose PO	14	1.03 (0.99, 1.08)	0.95 (0.92, 0.99)
itraconazole	200 mg once daily PO	480 mg once daily PO	14	0.76 (0.71, 0.81)	0.84 (0.76, 0.92)
posaconazole	300 mg single dose PO	480 mg once daily PO	13	0.98 (0.82, 1.17)	1.11 (0.95, 1.29)
voriconazole	200 mg twice daily PO	480 mg once daily PO	12	0.56 (0.51, 0.62)	0.61 (0.53, 0.71)
HMG-CoA Reductase Inhibitors					
atorvastatin	20 mg single dose PO	480 mg once daily PO	14	3.29 (2.84, 3.82)	2.17 (1.76, 2.67)
Oral Contraceptives					
ethinyl estradiol (EE) /levonorgestrel (LNG)	0.03 mg EE single dose PO	480 mg once daily PO	22	1.42 (1.32, 1.52)	0.89 (0.83, 0.96)
	0.15 mg LNG single dose PO		22	1.36 (1.30, 1.43)	0.95 (0.86, 1.04)

Abbreviations: PO=oral

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of letermovir have been characterised following oral and IV administration in healthy subjects and HSCT recipients and following oral administration in kidney transplant recipients.

Healthy Subjects

Letermovir exposure increased in a greater than dose-proportional manner with both oral or IV administration following single and multiple doses of 240 mg and 480 mg. Letermovir was absorbed rapidly with a median time to maximum plasma concentration (T_{max}) of 1.5 to 3.0 hours and declined in a biphasic manner. The geometric mean steady-state AUC and C_{max} values were 71,500 ng•hr/mL and 13,000 ng/mL, respectively, with 480 mg once daily oral PREVYMIS. The post-absorption plasma concentration-time profile of letermovir following oral administration was similar to the profile observed with IV dosing. Letermovir clearance (CL) reached steady-state in 9 to 10 days with an accumulation ratio of 1.22 for AUC and 1.03 for C_{max}.

The mean apparent terminal half-life for letermovir is approximately 12 hours with 480 mg IV PREVYMIS in healthy subjects.

HSCT Recipients
Letermovir AUC was estimated using population pharmacokinetic analyses using Phase 3 data (see Table 9). Differences in exposure across treatment regimens are not clinically relevant; efficacy was consistent across the range of exposures observed in P001.

Table 9: Letermovir AUC (ng•hr/mL) Values in HSCT Recipients

Treatment Regimen	Median (90% Prediction Interval)*
480 mg Oral, no ciclosporin	34,400 (16,900, 73,700)
480 mg IV, no ciclosporin	100,000 (65,300, 148,000)
240 mg Oral, with ciclosporin	60,800 (28,700, 122,000)
240 mg IV, with ciclosporin	70,300 (46,200, 106,000)
* Medians and 90% prediction intervals are based on simulations using the Phase 3 population PK model with inter-individual variability.	

Kidney Transplant Recipients
Letermovir AUC was estimated using population pharmacokinetic analysis using Phase 3 data (see Table 10). Efficacy was consistent across the range of exposures observed in P002.

Table 10: Letermovir AUC (ng•hr/mL) Values in Kidney Transplant Recipients

Treatment Regimen	Median (90% Prediction Interval)*
480 mg Oral, no cyclosporine	62,200 (28,900, 145,000)
240 mg Oral, with cyclosporine	57,700 (26,900, 135,000)
* Medians and 90% prediction intervals are based on simulations using the Phase 3 population PK model with inter-individual variability.	

Absorption
In healthy subjects, absolute bioavailability of letermovir was estimated to be approximately 94% over the dose range 240 mg to 480 mg based on population pharmacokinetic analyses. In HSCT recipients, bioavailability of letermovir was estimated to be approximately 35% with 480 mg once daily oral PREVYMIS administered without ciclosporin. The inter-individual variability for bioavailability was estimated to be approximately 37%. In kidney transplant recipients, bioavailability of letermovir was estimated to be approximately 60% with 480 mg once daily oral PREVYMIS administered without cyclosporine.

Effect of Ciclosporin
In HSCT recipients, co-administration of ciclosporin increased plasma concentrations of letermovir. Bioavailability of letermovir was estimated to be approximately 85% with 240 mg once daily oral PREVYMIS co-administered with ciclosporin. If PREVYMIS is co-administered with ciclosporin, the recommended dose of PREVYMIS is 240 mg once daily [see section 4.2, DOSE AND METHOD OF ADMINISTRATION].

Effect of Food
Relative to fasting conditions, oral administration of 480 mg single dose of PREVYMIS with a standard high fat and high calorie meal did not have any effect on the overall exposure (AUC) and resulted in approximately 30% increase in peak levels (Cmax) of letermovir. PREVYMIS may be administered orally with or without food [see section 4.2, DOSE AND METHOD OF ADMINISTRATION].

Distribution
Based on population pharmacokinetic analyses, the mean steady-state volume of distribution is estimated to be 45.5 L following IV administration in HSCT recipients.

Letermovir is extensively bound (98.7%) to human plasma proteins *in vitro*. Blood to plasma partitioning of letermovir is 0.56 and independent of the concentration range (0.1 to 10 mg/L) evaluated *in vitro*.

In preclinical distribution studies, letermovir is distributed to organs and tissues with the highest concentrations observed in the gastrointestinal tract, bile duct and liver and low concentrations in the brain.

Metabolism
The majority of drug-related component in plasma is unchanged parent (96.6%). No major metabolites are detected in plasma. Letermovir is partly eliminated by glucuronidation mediated by UGT1A1/1A3.

Excretion
Based on population pharmacokinetic analyses, letermovir steady-state CL is estimated to be 4.84 L/hr following IV administration in HSCT recipients. The inter-individual variability for CL is estimated to be 24.6%.

After oral administration of radio-labeled letermovir, 93.3% of radioactivity was recovered in feces. The majority of drug was excreted as unchanged parent with a minor amount (6% of dose) as an acyl-glucuronide metabolite in feces. Urinary excretion of letermovir was negligible (<2% of dose).

Specific Populations
Paediatric Population
The pharmacokinetics of letermovir in paediatric patients less than 18 years of age have not been evaluated.

Geriatric Population
Based on population pharmacokinetic analyses, there is no effect of age on letermovir pharmacokinetics. No dose adjustment is required based on age.

Gender
Based on population pharmacokinetic analyses, there is no difference in letermovir pharmacokinetics in females compared to males.

Weight
Based on Phase 1 population pharmacokinetic analyses, letermovir AUC is estimated to be 18.7% lower in subjects weighing 80-100 kg compared to subjects weighing 67 kg. Based on population pharmacokinetic analysis in kidney transplant recipients, letermovir AUC is estimated to be 26% lower in subjects weighing greater than 80 kg compared to subjects weighing less than or equal to 80 kg. These changes are not clinically relevant.

Race
Based on Phase 1 population pharmacokinetic analyses, letermovir AUC is estimated to be 33.2% higher in Asians compared to Whites. This change is not clinically relevant.

Renal Impairment
Clinical Study in a Renally Impaired Population
Letermovir AUC was approximately 1.9- and 1.4-fold higher in subjects with moderate (eGFR greater than or equal to 30 to 59 mL/min/1.73m2) and severe (eGFR less than 30 mL/min/1.73m2) renal impairment, respectively, compared to healthy subjects. The changes in letermovir exposure due to renal impairment are not clinically relevant. Given the minor role of renal excretion of letermovir, the mechanism by which this increased exposure occurs is not known.

Post-kidney Transplant
Based on population pharmacokinetic analysis, letermovir AUC was approximately 1.1-, 1.3- and 1.4-fold higher in subjects with mild (CrCl greater than or equal to 60 to less than 90 mL/min), moderate (CrCl greater than or equal to 30 to less than 60 mL/min) and severe (CrCl greater than or equal to 15 to less than 30 mL/min) renal impairment, respectively, compared to subjects with CrCl greater than or equal to 90 mL/min. These changes are not clinically relevant.

Hepatic Impairment
Letermovir AUC was approximately 1.6- and 3.8-fold higher in subjects with moderate (Child-Pugh Class B [CP-B], score of 7-9) and severe (Child-Pugh Class C [CP-C], score of 10-15) hepatic impairment, respectively, compared to healthy subjects. The changes in letermovir exposure in subjects with moderate hepatic impairment are not clinically relevant.

Clinically relevant increases in letermovir exposure are anticipated in patients with severe hepatic impairment or in patients with moderate hepatic impairment combined with moderate or severe renal impairment.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Letermovir was not genotoxic in a battery of *in vitro* or *in vivo* assays, including microbial mutagenesis assays, chromosomal aberration in Chinese Hamster Ovary cells, and in an *in vivo* mouse micronucleus study.

Carcinogenicity
A 6-month oral carcinogenicity study in RasH2 transgenic (Tg.RasH2) mice showed no evidence of human-relevant tumorigenesis up to the highest doses tested, 150 mg/kg/day (2 times the clinical plasma AUC at the maximum recommended human dose) and 300 mg/kg/day (6 times the clinical plasma AUC at the maximum recommended dose) in males and females, respectively.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablets
Tablet core
Microcrystalline cellulose
Croscarmellose sodium
Povidone
Silicon dioxide
Magnesium stearate

Film-coating
Lactose monohydrate
Hypromellose
Titanium dioxide
Triacetin
Iron oxide yellow
Iron oxide red (only for 480 mg tablets)
Carnauba wax (added as a polishing agent)

Concentrated Injection for Infusion
Hydroxypropylbetadex
Sodium chloride
Sodium hydroxide
Water for injections

6.2 INCOMPATIBILITIES

Incompatible Diluents, Drug Products, and Other Materials Used for Intravenous Administration
Incompatible Drug Products
PREVYMIS concentrated injection for infusion is physically incompatible with amiodarone hydrochloride, amphotericin B (liposomal), aztreonam, cefepime hydrochloride, ciprofloxacin, ciclosporin, diltiazem hydrochloride, filgrastim, gentamicin sulfate, levofloxacin, linezolid, lorazepam, midazolam HCl, mycophenolate mofetil hydrochloride, ondansetron, palonosetron.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

Incompatible IV Bags and Infusion Set Materials
PREVYMIS concentrated injection for infusion is incompatible with diethylhexyl phthalate (DEHP) plasticizers and polyurethane-containing IV administration set tubing.

This medicinal product must not be used with other IV bags and infusion set materials except those mentioned in section 4.2, DOSE AND METHOD OF ADMINISTRATION.

6.3 SHELF LIFE
In Australia, information on the shelf life can be found in 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

Tablets
Store PREVYMIS tablets in the original package until use.
Store PREVYMIS tablets below 30°C.

Concentrated injection for infusion
Store PREVYMIS concentrated injection for infusion vials below 25°C, limited excursions permitted between 15°C to 30°C. Store in the original carton to protect from light.

Storage of diluted solution
To reduce microbiological hazard, use as soon as practicable after preparation of diluted solution. If storage is necessary, the diluted solution can be stored for up to 24 hours at room temperature or up to 48 hours under refrigeration at 2°C to 8°C.
This time includes storage of the diluted solution in the intravenous bag through the duration of infusion.

6.5 NATURE AND CONTENTS OF CONTAINER

Tablets
The 240 mg film-coated tablets are packaged into a carton containing four (4) x 7-count Aluminium/Aluminium blister strips for a total of 28 tablets.

The 480 mg film-coated tablets are packaged into a carton containing four (4) x 7-count Aluminium/Aluminium blister strips for a total of 28 tablets.

Concentrated injection for infusion
Type I (30 mL) clear glass vial with a 20 mm chlorobutyl stopper containing 240 mg/12 mL or 480 mg/24 mL of solution.

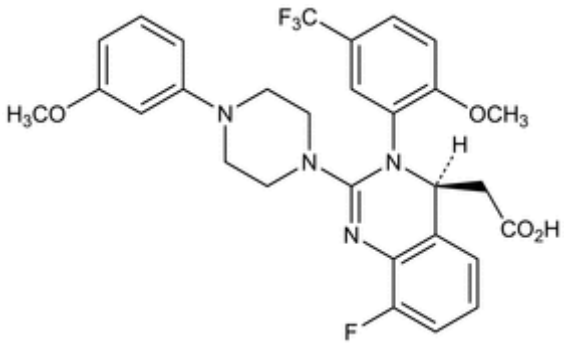
Pack size: 1 vial.

Not all presentations are available.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES
Letermovir has a molecular formula of C29H28F4N4O4 and a molecular weight of 572.55. The chemical name for letermovir is (4S)-2-{8-Fluoro-2-[4-(3- methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5- (trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid. Letermovir is very slightly soluble in water.

Chemical structure
The chemical structural formula is:



CAS number
The CAS Registry Number is 917389-32-3.

pKA and Partition coefficient
Letermovir drug substance (DS) is amorphous powder, with two pKa values at 3.6 and 7.1. The partition coefficient (Log P) at pH 7 is 2.17.

7 MEDICINE SCHEDULE (POISONS STANDARD)
Prescription only medicine (S4)

8 SPONSOR
Merck Sharp & Dohme (Australia) Pty Limited
Level 1, Building A, 26 Talavera Rd
Macquarie Park NSW 2113

Tel: (61) 02 8988 8000
www.msd-australia.com.au

9 DATE OF FIRST APPROVAL
Date of first inclusion in the Australian Register of Therapeutic Goods - 22 June 2018.

10 DATE OF REVISION
04 December 2024

Summary table of changes

Section changed	Summary of new information
4.1	Indication extended to include CMV Prophylaxis in Adult Kidney Transplant Recipients at high risk (Donor CMV seropositive/Recipient CMV seronegative [D+/R-])
4.2	Dosage instructions updated for the current indication of CMV Prophylaxis in Haematopoietic Stem Cell Transplant (HSCT) Recipients Updated Furosemide to sole ingredient name as per TGA guidance for IHIN

4.8	Additional adverse effects data added Kidney transplant indication and 200 day dosage for post-HSCT
4.9	Statement removed for clarity
5.1	Clinical trial data added regarding Kidney transplant indication and 200-day dosage for post-HSCT
5.2	Updated PK data added regarding Kidney transplant indication and 200-day dosage for post-HSCT
5.3	Carginogenicity data updated
All	Editorial changes - Updated table numbers and references - Addition of headers to help with clarity. - Other editorial changes

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