NEW ZEALAND DATA SHEET

1 PRODUCT NAME

PREVYMIS® letermovir 240 mg film coated tablet
PREVYMIS® letermovir 480 mg film coated tablet
PREVYMIS® letermovir 240 mg/12mL concentrated injection for infusion
PREVYMIS® letermovir 480 mg/24mL concentrated injection for infusion

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.

Concentrated injection for infusion

Each single-dose vial contains 240 mg (12 mL per vial) or 480 mg (24 mL per vial) of letermovir.
Each mL contains 20 mg 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.

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 in a single-dose vial.

PREVYMIS 480 mg/24 mL (20 mg/mL) concentrated injection for infusion is supplied as a clear solution in a single-dose vial.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

PREVYMIS is indicated for the prophylaxis of cytomegalovirus (CMV) infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT).

4.2 Dose and method of administration

The recommended dosage of PREVYMIS is 480 mg administered once daily.

PREVYMIS should be started after HSCT. PREVYMIS may be started on the day of transplant and no later than 28 days post-transplant. PREVYMIS may be started before or after engraftment. Continue PREVYMIS through 100 days post-transplant.

PREVYMIS Film coated tablets

- Administer with or without food.
- Swallow tablets whole. Do not divide, crush or chew.

PREVYMIS Concentrated injection for infusion

- 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.].

- 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].

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

Renal impairment
No dose adjustment of PREVYMIS is required based on renal impairment [see section 5.2].

Elderly
No dose adjustment of PREVYMIS is required based on age [see section 5.2].

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

Method of Administration

- 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.

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].

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 sections 4.5].

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 sections 4.4 and 4.5].

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 sections 4.3 and 4.5].

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].

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].

PREVYMIS is not recommended in patients with moderate hepatic impairment combined with moderate

or severe renal impairment [see section 4.2].

Use in renal impairment

No dose adjustment of PREVYMIS is required based on renal impairment [see section 4.2]. 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 trial in HSCT 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 interaction

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].

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).

Rifampin co-administration resulted in an initial increase in letermovir plasma concentrations (due to OATP1B1/3 inhibition) that is not clinically relevant, followed by clinically relevant decreases in letermovir plasma concentrations with continued rifampin co-administration [see Table 5 in section 5.1]

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] 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].

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	Co-administration of PREVYMIS with phenytoin

	↓ 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.
rifampin[‡]	↓ letermovir	Co-administration of PREVYMIS with rifampin decreases plasma concentrations of letermovir. Co-administration of PREVYMIS and rifampin is not recommended.
Antipsychotics		
pimozide	↑ pimozide	Co-administration is contraindicated due to risk of QT prolongation and torsades de pointes [see section 4.3].
thioridazine	↓ letermovir	Co-administration of PREVYMIS with thioridazine may decrease plasm 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].
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].
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]. 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].

* 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 5 and Table 6).

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

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).

Breast-feeding

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.

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 trial in HSCT recipients, there was no evidence of letermovir-related testicular toxicity [see section 4.8].

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.

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 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.

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

Post-Marketing Experience

Reporting suspected adverse effects
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at https:nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

There is no 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

Pharmacotherapeutic group: Antivirals for systemic use, direct acting antivirals, ATC code: J05AX18

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 Hematopoietic Stem Cell Transplant

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-transplant) and continued through Week 14 post-transplant. 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-transplant for the primary efficacy endpoint with continued follow-up through Week 48 post-transplant.

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-transplant. 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-transplant or had a missing outcome at Week 24 post-transplant 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)

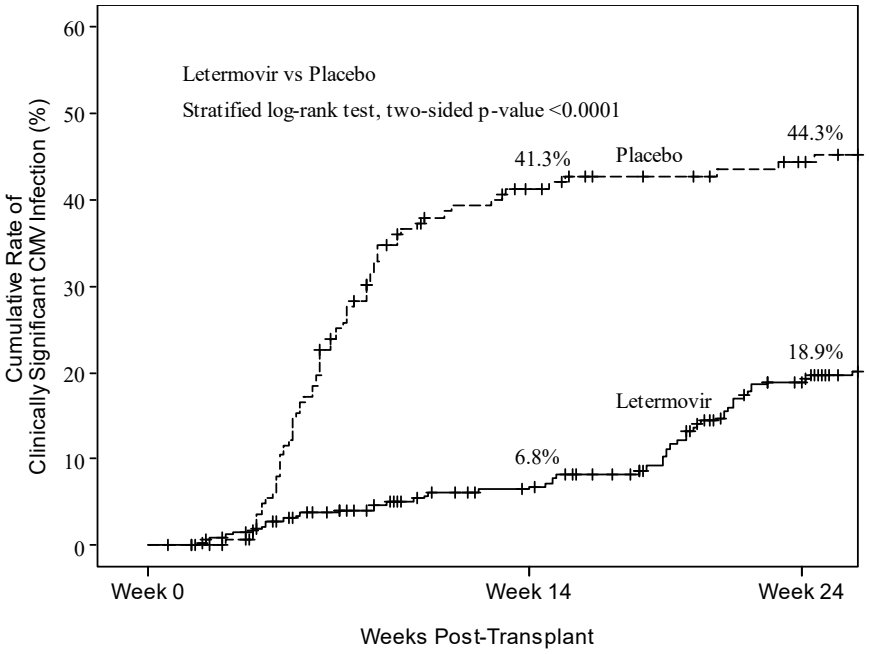
Parameter	**PREVYMIS (N=325) n (%)**	**Placebo (N=170) n (%)**
Primary Endpoint (Proportion of subjects who failed prophylaxis)	**122 (37.5)**	**103 (60.6)**
Reasons for Failures*		
Clinically significant CMV infection by Week 24†	57 (17.5)	71 (41.8)
Initiation of PET based on documented CMV viraemia	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-transplant 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 viremia 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-transplant. 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-transplant, 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-transplant 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.

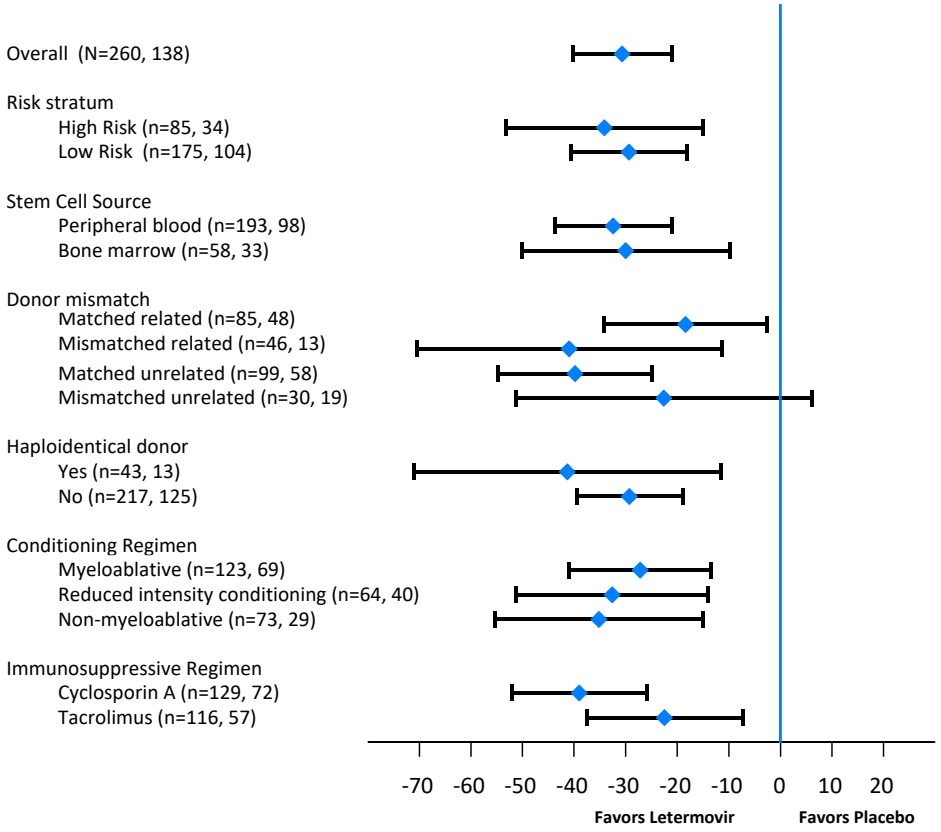
Figure 1: P001: Kaplan-Meier Plot of Time to Onset of Clinically Significant CMV Infection Through Week 24 Post-Transplant in HSCT Recipients (FAS Population)



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-Transplant by Selected Subgroups (DAO Approach, FAS Population)

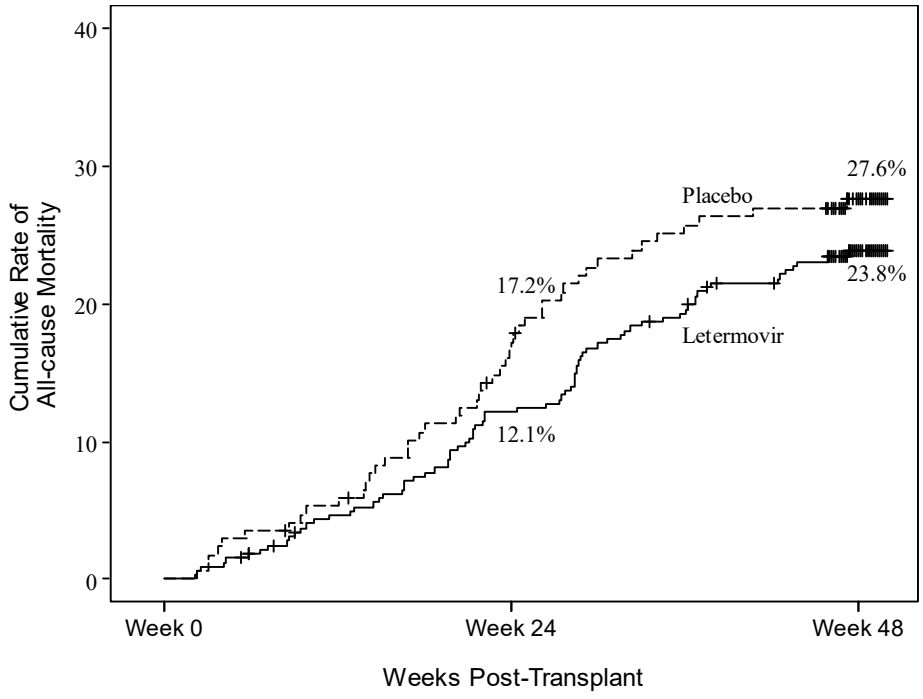


DAO= data as observed. With DAO approach, any subject with a missing value was excluded from the analysis.

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-transplant (nominal two-sided stratified log-rank p-value=0.0401), and 23.8% vs. 27.6% at Week 48 post-transplant (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

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 andthe substitutions map to pUL51 (P91S), 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 subsitutionV236M, 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 exposures.

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 5 and Table 6).

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]. 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 rifampin 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], Table 1 and Table 5. 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 6). Based on these results, co-administration of PREVYMIS with CYP3A substrates may increase the plasma concentrations of the CYP3A substrates [see sections 4.3 4.4and 4.5] 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 6). The effect of letermovir on BCRP, BSEP, and MRP2 substrates was not evaluated in clinical studies; the clinical relevance is unknown.

Table 5: 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					
rifampin	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, 1.28)
	600 mg once daily PO (24 hours after rifampin) †	480 mg once daily PO	14	0.15 (0.13, 0.17)	0.27 (0.22, 0.31)
Immunosuppressants					
ciclosporin	200 mg single dose PO	240 mg once daily PO	12	2.11 (1.97, 2.26)	1.48 (1.33, 1.65)
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 rifampin on letermovir 24 hours after the final rifampin dose.
C24 GMR [90%] is 0.09 (0.06, 0.12).

Table 6: 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)

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
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					
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.

In 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}.

In HSCT recipients, letermovir AUC was estimated using population pharmacokinetic analyses using Phase 3 data (see Table 7). Differences in exposure across treatment regimens are not clinically relevant; efficacy was consistent across the range of exposures observed in P001.

Table 7: 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	

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%.

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].

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].

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.

Biotransformation

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.

Elimination

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

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 population pharmacokinetic analyses, letermovir AUC is estimated to be 18.7% lower in subjects weighing 80-100 kg compared to subjects weighing 67 kg. This change is not clinically relevant.

Race
Based on 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
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.

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

Carcinogenicity studies with letermovir have not been conducted.

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.

Incompatible IV Bags and Infusion Set Materials
PREVYMIS concentrated injection for infusion is incompatible with 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.

6.3 Shelf life

Tablets
36 months

Concentrated injection for infusion
36 months

Storage of diluted solution

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C and for 48 hours at 2 to 8°C.

From a microbial point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

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.

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 and other handling

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. Do not use the vial if the solution is discolored or contains visible particles.
- 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, whenever solution and container permit. Discard if discoloration or visible particles are observed.

Administration
See section 4.2

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 (frusemide)
- 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].

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

diethylhexyl-phthalate (DEHP), tris (2-Ethylhexyl) trimellitate (TOTM), butyl benzyl phthalate (BBP)

Catheters
Radiopaque polyurethane

Any unused medicine or waste material should be disposed of by taking to your local pharmacy.

7 MEDICINE SCHEDULE

Prescription only medicine

8 SPONSOR

Merck Sharp & Dohme (New Zealand) Ltd
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9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:

24 September 2020

10 DATE OF REVISION OF THE TEXT

14 November 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.5	Added text regarding strong and moderate inducers. Table 1: Added rows for strong and moderate inducers. Added itraconazole and fluconazole.
5.1	Updated Viral Resistance and Cross Resistance
5.1	Updated Drug Interaction Studies: - Added text regarding strong and moderate inducers. - Added itraconazole. - Table 5: Added rifampin, itraconazole and fluconazole. - Table 6: Added itraconazole and fluconazole