Prevymis F.C. Tablets 240mg and 480mg
Prevymis Concentrate for Solution for Infusion 20mg/mL

1 Description

PREVYMIS contains letermovir, an inhibitor of the CMV DNA terminase complex, and is administered orally or by intravenous infusion.

1.1 Active Ingredients and Strengths

PREVYMIS is available as 240 mg and 480 mg tablets.

PREVYMIS is also available as 240 mg and 480 mg injection for intravenous infusion.

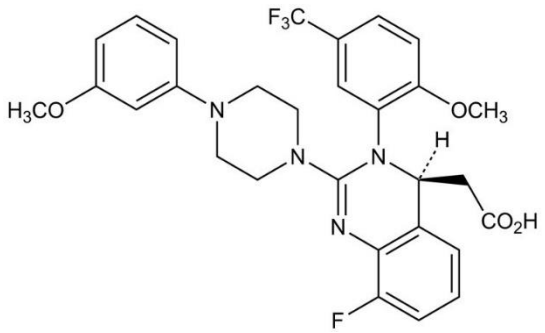
Active Ingredient

PREVYMIS tablets contain either 240 mg or 480 mg of letermovir.

PREVYMIS concentrate for solution for infusion is a clear, preservative-free sterile solution and may contain a few small translucent or white particles in single-dose vials of either 240 mg or 480 mg per vial. Each 1 mL of solution contains 20 mg letermovir.

Letermovir has a molecular formula of $C_{29}H_{28}F_4N_4O_4$ and a molecular weight of 572.55. The chemical name for letermovir is (4*S*)-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.

The chemical structure of letermovir is:



1.2 Excipients

PREVYMIS tablets contain the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, povidone 25, silica, colloidal anhydrous, magnesium stearate and film-coated with a coating material containing the following inactive ingredients: lactose monohydrate, hypromellose 2910, titanium dioxide, triacetin, iron oxide yellow, and (only for 480 mg tablets) iron oxide red. Carnauba wax is added as a polishing agent.

Each 1 mL of PREVYMIS concentrate for solution for infusion contains the following inactive ingredients: hydroxypropyl betadex (150 mg), sodium chloride (3.1 mg), sodium hydroxide (1.2 mg), and Water for Injection.

The amount of sodium hydroxide may be adjusted to achieve a pH of approximately 7.5.

1.3 Dosage Forms

Tablets

- PREVYMIS 240 mg tablet
- PREVYMIS 480 mg tablet

Injection

- PREVYMIS 240 mg/12 mL (20 mg/mL) injection
- PREVYMIS 480 mg/24 mL (20 mg/mL) injection

1.4 Appearance

Tablets

- PREVYMIS 240 mg tablet: yellow oval tablet with “591” on one side and corporate logo on the other side.
- PREVYMIS 480 mg tablet: pink oval, bi-convex tablet with “595” on one side and corporate logo on the other side.

Injection

- PREVYMIS 240 mg/12 mL (20 mg/mL) injection: clear solution in a single-dose vial.
- PREVYMIS 480 mg/24 mL (20 mg/mL) injection: clear solution in a single-dose vial.

2 Indication

2.1 Indicated for prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV- seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT).

2.2 Indicated for prophylaxis of CMV disease in adult kidney transplant recipients at high risk (Donor CMV seropositive/Recipient CMV seronegative [D+/R-]).

3 Dosage and Administration

3.1 Dosage and Administration

PREVYMIS™ Tablets

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

PREVYMIS™ Injection

- 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 at a constant rate over 1 hour.
- Do not administer as an intravenous bolus injection.

3.1.1 Recommended Dosage for Adult Patients

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

Dosage of PREVYMIS should be adjusted when co-administered with cyclosporine *[see Dosage and Administration (3.3)].*

PREVYMIS injection, which contains hydroxypropyl betadex, should be used only in patients unable to take oral therapy. Patients should be switched to oral PREVYMIS as soon as they are able to take oral medications. PREVYMIS tablet and injection may be used interchangeably at the discretion of the physician, and no dosage adjustment is necessary when switching formulations.

<u>HSCT</u>

Initiate PREVYMIS between Day 0 and Day 28 post-HSCT (before or after engraftment), and continue through Day 100 post-HSCT. In patients at risk for late CMV infection and disease, PREVYMIS may be continued through Day 200 post-HSCT.

<u>Kidney Transplant</u>

Initiate PREVYMIS between Day 0 and Day 7 post-kidney transplant and continue through Day 200 post-transplant.

3.2 Reconstitution methods

3.2.1 Preparation and Administration of Intravenous Solution

PREVYMIS injection is supplied in 30 mL single-dose vials containing either 240 mg/12 mL per vial (20 mg/mL) or 480 mg/24 mL per vial (20 mg/mL). The preparation and administration instructions are the same for either dose.

PREVYMIS vials are for single use only. Discard any unused portion.

Preparation and Administration Instructions

- PREVYMIS must be diluted prior to intravenous (IV) use.
- Inspect vial contents for discoloration and particulate matter prior to dilution. PREVYMIS injection 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 injection 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 injection into a 250 mL pre-filled IV bag containing either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP and mix bag gently. Do not shake. Only 0.9% Sodium Chloride and 5% Dextrose are chemically and physically compatible with PREVYMIS injection.
- Use compatible IV bags and infusion set materials. PREVYMIS injection is compatible with the following IV bags and infusion set materials. PREVYMIS injection is not recommended with any IV bags or infusion set materials not listed below (note that PREVYMIS injection is not recommended for use with polyurethane-containing IV administration set tubing).

IV Bags Materials:

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

Infusion Sets 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), benzyl butyl phthalate (BBP)

Catheters:

Radiopaque polyurethane

- 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. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.
- Discard if the diluted solution is cloudy, discolored, or contains matter other than a few small translucent or white particles.
- The diluted solution is stable for up to 24 hours at room temperature or up to 48 hours under refrigeration at 2°C to 8°C (36°F to 46°F) (this time includes storage of the diluted solution in the intravenous bag through the duration of infusion).

- 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 the entire contents of the intravenous bag by intravenous infusion via a peripheral catheter or central venous line at a constant rate over 1 hour *[see Dosage and Administration (3.1)]*.

3.2.2 Compatible Drug Products Used for Intravenous Administration

Compatible Drug Products

The physical compatibility of PREVYMIS injection with selected injectable drug products was evaluated in two commonly available diluents. PREVYMIS should not be co-administered through the same intravenous line (or cannula) with other drug products and diluent combinations except those listed below. Refer to the respective prescribing information of the co-administered drug(s) to confirm compatibility of simultaneous co-administration.

List of Compatible Drug Products when PREVYMIS and Drug Products are Prepared in 0.9% Sodium Chloride Injection, USP:

Ampicillin sodium, ampicillin sodium/sulbactam sodium, anti-thymocyte globulin, caspofungin, daptomycin, fentanyl citrate, fluconazole, furosemide, human insulin, magnesium sulfate, methotrexate, micafungin.

List of Compatible Drug Products when PREVYMIS and Drug Products are Prepared in 5% Dextrose Injection, USP:

Amphotericin B (lipid complex)*, anidulafungin, cefazolin sodium, ceftaroline, ceftriaxone sodium, doripenem, famotidine, folic acid, ganciclovir sodium, hydrocortisone sodium succinate, morphine sulfate, 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 *Reconstitution methods* (3.2.3)].

3.2.3 Incompatible Drug Products and Other Materials Used for Intravenous Administration

Incompatible Drug Products

PREVYMIS injection is physically incompatible with amiodarone hydrochloride, amphotericin B (liposomal), aztreonam, cefepime hydrochloride, ciprofloxacin, cyclosporine, diltiazem hydrochloride, filgrastim, gentamicin sulfate, levofloxacin, linezolid, lorazepam, midazolam HCl, mycophenolate mofetil hydrochloride, ondansetron, palonosetron.

Incompatible IV Bags and Infusion Set Materials

PREVYMIS concentrate for solution for infusion is incompatible with diethylhexyl phthalate (DEHP) plasticizers and polyurethane-containing IV administration set tubing.

3.3 Specific Populations Dosage and Administration

3.3.1 Dosage Adjustment When Co-administered with Cyclosporine

If oral or intravenous PREVYMIS is co-administered with cyclosporine, the dosage of PREVYMIS should be decreased to 240 mg once daily *[see Interactions (7.1, 7.2, 7.3) and Pharmacokinetics (11)].*

- If cyclosporine is initiated after starting PREVYMIS, the next dose of PREVYMIS should be decreased to 240 mg once daily.
- If cyclosporine is discontinued after starting PREVYMIS, the next dose of PREVYMIS should be increased to 480 mg once daily.
- If cyclosporine dosing is interrupted due to high cyclosporine levels, no dose adjustment of PREVYMIS is needed.

3.3.2 Use in Patients with Renal Impairment

- For patients with creatinine clearance (CLcr) greater than 10 mL/min, no dosage adjustment of PREVYMIS is required based on renal impairment *[see Warnings in Special Populations (6.7), and Pharmacokinetics (11)].*
- There are insufficient data in patients with CLcr 10 mL/min or less or in patients on dialysis to make PREVYMIS dosing recommendations.
- In patients with CLcr less than 50 mL/min receiving PREVYMIS injection, accumulation of the intravenous vehicle, hydroxypropyl betadex, may occur. Closely monitor serum creatinine levels in these patients.

3.3.3 Use in Patients with Hepatic Impairment

No dosage adjustment of PREVYMIS is required for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. PREVYMIS is not recommended for patients with severe (Child- Pugh Class C) hepatic impairment *[see Warnings in Special Populations (6.6)]*.

3.4 Patient Monitoring

Following the completion of PREVYMIS prophylaxis in HSCT patients, monitoring for CMV reactivation is recommended.

4 Contraindications

- PREVYMIS is contraindicated in patients receiving pimozide or ergot alkaloids:
    - Pimozide: Concomitant administration of PREVYMIS in patients receiving pimozide may result in increased concentrations of pimozide due to inhibition of cytochrome P450 3A (CYP3A) by letermovir, which may lead to QT prolongation and torsades de pointes *[see Warnings and Precautions (5.1) and Interactions (7.2, 7.3)]*.
    - Ergot alkaloids: Concomitant administration of PREVYMIS in patients receiving ergot alkaloids may result in increased concentrations of ergot alkaloids (ergotamine and dihydroergotamine) due to inhibition of CYP3A by letermovir, which may lead to ergotism *[see Warnings and Precautions (5.1) and Interactions (7.2, 7.3)]*.
- PREVYMIS is contraindicated with pitavastatin and simvastatin when co-administered with cyclosporine. Concomitant administration of PREVYMIS in combination with cyclosporine may result in significantly increased pitavastatin or simvastatin concentrations, which may lead to myopathy or rhabdomyolysis *[see Warnings and Precautions (5.1) and Interactions (7.2, 7.3)].*

5 Warnings and Precautions

5.1 Warnings/Precautions

Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions

The concomitant use of PREVYMIS and certain drugs may result in potentially significant drug interactions, some of which may lead to adverse reactions (PREVYMIS or concomitant drugs) or reduced therapeutic effect of PREVYMIS or the concomitant drug *[see Contraindications (4) and Interactions (7.1, 7.2, 7.3)].*

See Table 1 for steps to prevent or manage these possible or known significant drug interactions. Consider the potential for drug interactions prior to and during PREVYMIS therapy; review concomitant medications during PREVYMIS therapy; and monitor for adverse reactions associated with PREVYMIS and concomitant medications.

6 Warnings in Special Populations

6.1 Pregnancy

Risk Summary

No adequate human data are available to establish whether PREVYMIS poses a risk to pregnancy outcomes. In animal reproduction studies, embryo-fetal developmental toxicity (including fetal malformations) was observed in rats during the period of organogenesis at letermovir exposures (AUC) 11 times higher than human exposure at the recommended human dose (RHD). In rabbits, spontaneous abortion, increased loss after implantation, and skeletal abnormality as an embryo-fetal developmental toxicity were noted at exposures that were maternally toxic (up to letermovir exposures 2 times higher than human exposure at the RHD). In a rat pre/post-natal development study, total litter loss was observed at maternal letermovir exposures approximately 2 times higher than human exposure at the RHD *(see Data)*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Letermovir was administered orally to pregnant rats at 0, 10, 50 or 250 mg/kg/day from gestation days 6 to 17. Developmental toxicities, including skeletal malformations and umbilical cord shortening, were observed at 250 mg/kg/day (approximately 11 times higher than human exposure at the RHD). In addition, decreased fetal body weight and skeletal variations (due to maternal toxicity) were observed at this dose. No embryo-fetal toxicities were observed at 50 mg/kg/day (approximately 3 times higher than human exposure 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. Developmental toxicities, including spontaneous abortion, increased post-implantation loss, and skeletal variations, were observed at a maternally toxic dose (225 mg/kg/day; approximately 2 times higher than human exposure at the RHD). No embryo-fetal toxicities were observed at 75 mg/kg/day (less than human exposure at the RHD).

In the pre/post-natal development 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. At 180 mg/kg/day (approximately 2 times higher than human exposure at the RHD), total litter loss due to stillbirth or possible maternal neglect was observed in 5 of 23 pregnant females by post-partum/lactation day 4. In surviving offspring, slight developmental delays in vaginal opening and pinna unfolding were accompanied by reduced body weight gain at this dose. No toxicities were observed at 45 mg/kg/day (similar to human exposure at the RHD).

6.2 Lactation

Risk Summary

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 the milk of lactating rats as well as the blood of nursing pups *(see Data)*.

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.

Data

In a lactation study, letermovir was excreted in milk when administered intravenously (at 10 mg/kg) to lactating rats on post-partum/lactation day 10. Letermovir was also detected in the blood of nursing pups on post-partum/lactation day 21 in the pre/post-natal developmental study.

6.3 Females and Males of Reproductive Potential

Infertility

There are no data on the effect of letermovir on human fertility. Decreased fertility due to testicular toxicity was observed in male rats *[see Clinical Pharmacology (10.3)]*.

6.4 Pediatric use

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

6.5 Geriatric use

Of the 373 subjects treated with PREVYMIS in Trial P001, 56 (15%) subjects were 65 years of age or older. Of the 144

subjects treated with PREVYMIS in Trial P040, 32 (22%) subjects were 65 years of age or older. Of the 292 subjects treated with PREVYMIS in Trial P002, 48 (16%) subjects were 65 years of age or older. Safety and efficacy were similar across older and younger subjects in each trial. No dosage adjustment of PREVYMIS is required based on age *[see Pharmacokinetics (11)].*

6.6 Patients with Hepatic Impairment

No dosage adjustment of PREVYMIS is required for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. PREVYMIS is not recommended for patients with severe (Child- Pugh Class C) hepatic impairment *[see Pharmacokinetics (11)]*.

6.7 Patients with Renal Impairment

For patients with CLcr greater than 10 mL/min (by Cockcroft-Gault equation), no dosage adjustment of PREVYMIS is required based on renal impairment *[see Pharmacokinetics (11)].* The safety of PREVYMIS in patients with end-stage renal disease (CLcr less than 10 mL/min), including patients on dialysis, is unknown.

In patients with CLcr less than 50 mL/min receiving PREVYMIS injection, accumulation of the intravenous vehicle, hydroxypropyl betadex, could occur. Closely monitor serum creatinine levels in these patients.

7 Interactions

7.1 Potential for Other Drugs to Affect 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 (Table 1).

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. Examples of strong inducers include rifampin, rifabutin, phenytoin, phenobarbital, carbamazepine, St. John's wort (*Hypericum perforatum*) and examples of moderate inducers include nafcillin, thioridazine, modafinil, bosentan, efavirenz, etravirine and nevirapine *(see Table 1)*.

Rifampin co-administration resulted in an initial increase in letermovir plasma concentrations (due to OATP1B1/3 inhibition) that is not considered clinically relevant, followed by clinically relevant decreases in letermovir plasma concentrations with continued rifampin co-administration *[see Table 7 in Pharmacokinetics (11)]*.

7.2 Potential for PREVYMIS to Affect Other Drugs

Co-administration of PREVYMIS with midazolam results in increased midazolam plasma concentrations, indicating that letermovir is a moderate inhibitor of CYP3A *[see Pharmacokinetics (11)]*. 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 (Table 1) *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

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 (Table 1).

The magnitude of CYP3A- and OATP1B1/3-mediated drug interactions on co-administered drugs may be different when PREVYMIS is co-administered with cyclosporine. See the prescribing information for cyclosporine for information on drug interactions with cyclosporine.

7.3 Established and Other Potentially Significant 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.

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 Contraindications (4), Warnings and Precautions (5.1), and Pharmacokinetics (11)]*.

Table 1: Potentially Significant Drug Interactions: Alteration in Dose May Be Recommended Based on Results from Drug Interaction Studies or Predicted Interactions* (Information in the Table Applies to Co-administration of PREVYMIS and the Concomitant Drug without Cyclosporine, Unless Otherwise Indicated)

Concomitant Drug Class and/or Clearance Pathway: Drug Name	**Effect on Concentration†**	**Clinical Comments**
Anti-arrhythmic Agents		
amiodarone	↑ amiodarone	Close clinical monitoring for adverse events related to amiodarone is recommended during co- administration. Frequently monitor amiodarone concentrations when amiodarone is co- administered with PREVYMIS.
Antibiotics		
nafcillin	↓ letermovir	Co-administration of PREVYMIS and nafcillin is not recommended.
Anticoagulants		
warfarin	↓ warfarin	When PREVYMIS is co-administered with warfarin, frequently monitor International Normalized Ratio (INR) ‡.
Anticonvulsants		
carbamazepine	↓ letermovir	Co-administration of PREVYMIS and carbamazepine is not recommended.
phenobarbital	↓ letermovir	Co-administration of PREVYMIS and phenobarbital is not recommended.
phenytoin	↓ letermovir ↓ phenytoin	Co-administration of PREVYMIS and phenytoin is not recommended.
Antidiabetic Agents		
Examples: glyburide, repaglinide, rosiglitazone	↑ glyburide ↑ repaglinide ↑ rosiglitazone	When PREVYMIS is co-administered with glyburide, repaglinide, or rosiglitazone, frequently monitor glucose concentrations‡. When PREVYMIS is co-administered with cyclosporine, use of repaglinide is not recommended.
Antifungals		
voriconazole§	↓ voriconazole	If concomitant administration of voriconazole is necessary, closely monitor for reduced effectiveness of voriconazole‡.
Antimycobacterials		
rifabutin	↓ letermovir	Co-administration of PREVYMIS and rifabutin is not recommended.
rifampin§	↓ 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 Contraindications (4)*].
thioridazine	↓ letermovir	Co-administration of PREVYMIS and thioridazine is not recommended.
Endothelin Antagonists		
bosentan	↓ letermovir	Co-administration of PREVYMIS and bosentan is not recommended.
Herbal Products		
St. John's wort (*Hypericum perforatum*)	↓ letermovir	Co-administration of PREVYMIS and St. John's wort is not recommended.
HIV Medications		
efavirenz	↓ letermovir	Co-administration of PREVYMIS and efavirenz is not recommended.
etravirine	↓ letermovir	Co-administration of PREVYMIS and etravirine is not recommended.
nevirapine	↓ letermovir	Co-administration of PREVYMIS and nevirapine is not recommended.
Ergot alkaloids		
ergotamine, dihydroergotamine	↑ ergotamine, dihydroergotamine	Co-administration is contraindicated due to risk of ergotism *[see Contraindications (4)].*
HMG-CoA Reductase Inhibitors		
atorvastatin§	↑ atorvastatin	When PREVYMIS is co-administered with atorvastatin, do not exceed an atorvastatin dosage of 20 mg daily§. Closely monitor patients for myopathy and rhabdomyolysis. When PREVYMIS is co-administered with cyclosporine, use of atorvastatin is not recommended.
pitavastatin, simvastatin	↑ HMG-CoA reductase inhibitors	Co-administration of PREVYMIS and pitavastatin or simvastatin is not recommended. When PREVYMIS is co-administered with cyclosporine, use of either pitavastatin or simvastatin is contraindicated due to significantly increased pitavastatin or simvastatin concentrations and risk of myopathy or rhabdomyolysis *[see Contraindications (4)]*.

fluvastatin, lovastatin, pravastatin, rosuvastatin	↑ HMG-CoA reductase inhibitors	When PREVYMIS is co-administered with these statins, a statin dosage reduction may be necessary‡. Closely monitor patients for myopathy and rhabdomyolysis. When PREVYMIS is co-administered with cyclosporine, use of lovastatin is not recommended. When PREVYMIS is co-administered with cyclosporine, refer to the statin prescribing information for specific statin dosing recommendations.
Immunosuppressants		
cyclosporine§	↑ cyclosporine ↑ letermovir	Decrease the dosage of PREVYMIS to 240 mg once daily *[see Dosage and Administration (3.3.1) and Pharmacokinetics (11)]*. Frequently monitor cyclosporine whole blood concentrations during treatment and after discontinuation of PREVYMIS and adjust the dose of cyclosporine accordingly‡.
sirolimus§	↑ sirolimus	When PREVYMIS is co-administered with sirolimus, frequently monitor sirolimus whole blood concentrations during treatment and after discontinuation of PREVYMIS and adjust the dose of sirolimus accordingly‡. When PREVYMIS is co-administered with cyclosporine and sirolimus, refer to the sirolimus prescribing information for specific sirolimus dosing recommendations‡.
tacrolimus§	↑ tacrolimus	Frequently monitor tacrolimus whole blood concentrations during treatment and after discontinuation of PREVYMIS and adjust the dose of tacrolimus accordingly‡.
Proton Pump Inhibitors		
omeprazole	↓omeprazole	Clinical monitoring and dose adjustment may be needed.
pantoprazole	↓ pantoprazole	Clinical monitoring and dose adjustment may be needed.
Wakefulness-Promoting Agents		
modafinil	↓ letermovir	Co-administration of PREVYMIS and modafinil is not recommended.
CYP3A Substrates		

Examples: alfentanil, fentanyl, midazolam, and quinidine	↑ CYP3A substrate	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[§]. When PREVYMIS is co-administered with cyclosporine, 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[§]. CYP3A substrates pimozide and ergot alkaloids are contraindicated *[see Contraindications (4)].*
* This table is not all inclusive. † ↓ =decrease, ↑=increase ‡ Refer to the respective prescribing information. § These interactions have been studied *[see Pharmacokinetics (11)]*.		

7.4 Drugs without Clinically Significant Interactions with PREVYMIS

No clinically significant interactions were observed in clinical drug-drug interaction studies of letermovir and acyclovir, digoxin, mycophenolate mofetil, fluconazole, itraconazole, posaconazole, ethinyl estradiol, and levonorgestrel.

8 Adverse Reactions/ Undesirable effects

8.1 Clinically Significant Adverse Reactions

No information.

8.2 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction 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

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

The safety of PREVYMIS was evaluated in a Phase 3 randomized, double-blind, placebo-controlled trial (P001) in which 565 subjects were randomized 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-assessed 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%
diarrhea	26%	24%
vomiting	19%	14%
peripheral edema	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 dyspnea, 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 randomized, double-blind, placebo-controlled trial (P040) in which 218 subjects who completed PREVYMIS prophylaxis through ~100 days post-HSCT were randomized 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 diarrhea (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, diarrhea, 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%).

Laboratory Abnormalities

Selected laboratory abnormalities reported through Week 28 post-transplant are presented in the table below.

Table 4: Trial P002 Selected Laboratory Abnormalities

	PREVYMIS N=292	**Valganciclovir N=297**
Absolute neutrophil count (cells/μL)		
< 500	2%	7%
500 – < 750	1%	2%
750 – < 1000	1%	7%
Hemoglobin (g/dL)		
< 6.5	1%	0%
6.5 – < 8.0	4%	4%
8.0 – < 9.5	30%	32%
Platelets (cells/μL)		
< 25000	0%	0%
25000 – < 50000	0%	0%
50000 – < 100000	1%	3%
Leukocytes (cells/μL)		

< 1000	1%	2%
1000 – < 2000	5%	16%
2000 – < 3500	16%	36%
Serum creatinine (mg/dL)		
> 2.5	22%	21%
> 1.5 – 2.5	51%	52%

8.3 Post-marketing Experience

None

9 Overdose

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 be instituted.

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

10 Clinical Pharmacology

10.1 Mechanism of action

PREVYMIS is an antiviral drug against CMV *[see Microbiology (10.2.1)]*.

10.2 Pharmacodynamics

Cardiac Electrophysiology

In a thorough QT trial in healthy subjects, letermovir at the therapeutic IV dose or at a dose of 2 times the approved IV dose did not prolong QTc to any clinically relevant extent.

10.2.1 Microbiology

Mechanism of Action

Letermovir inhibits the CMV DNA terminase complex (pUL51, pUL56, and pUL89) which is required for viral DNA processing and packaging. Biochemical characterization and electron microscopy demonstrated that letermovir affects the production of proper unit length genomes and interferes with virion maturation. Genotypic characterization of virus resistant to letermovir confirmed that letermovir targets the terminase complex.

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 (0.7 nM to 6.1 nM, n = 74). There was no significant difference in EC_{50} value by CMV gB genotype (gB1=29; gB2=27; gB3=11; and gB4=3).

Combination Antiviral Activity

No antagonism of the antiviral activity was seen when letermovir was combined with CMV DNA polymerase inhibitors (cidofovir, foscarnet, or ganciclovir).

Viral Resistance

In Cell Culture

CMV mutants with reduced susceptibility to letermovir have been selected in cell culture and the resistance mutations map to UL51, UL56, and UL89. Resistance-associated substitutions were found in pUL51 (P91S, A95V), pUL56 (C25F, S229F, V231A/L, N232Y, V236A/L/M, E237D, L241P, T244K/R, L254F, L257F/I, K258E, F261C/L/S, Y321C, C325F/R/W/Y, L328V, M329T, A365S, N368D, R369G/M/S), 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 or placebo 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 on-treatment samples were available for analysis. One subject had a letermovir resistance substitution, pUL56 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 50 letermovir-treated subjects who had received at least one dose of study drug and experienced prophylaxis failure and for whom samples were available for analysis. A total of 4 resistance-associated substitutions all mapping to pUL56 were detected in 3 subjects as follows: V236M, C325W and R369T, and E237G; however, no 2 subjects had substitutions at the same positions.

In a Phase 3 trial (P040), DNA sequence analysis of the entire coding regions of UL51, UL56 and UL89 was performed on samples obtained from 32 subjects (regardless of treatment group) who experienced prophylaxis failure or who discontinued early with CMV viremia. There were no letermovir resistance-associated substitutions detected above the validated assay limit.

In a Phase 3 trial (P002), DNA sequence analysis of the entire coding regions of UL51, UL56 and UL89 was performed on samples obtained from 52 letermovir-treated subjects who experienced CMV disease or who discontinued early with CMV viremia. There were no letermovir resistance-associated substitutions detected above the validated assay limit.

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 (cidofovir, foscarnet, and ganciclovir). These DNA polymerase inhibitors are fully active against viral populations with substitutions conferring resistance to letermovir.

10.3 Preclinical safety data

10.3.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Letermovir was not genotoxic in *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.

Letermovir was not carcinogenic in a 6-month RasH2 transgenic mouse study up to the highest doses tested (150 mg/kg/day in males and 300 mg/kg/day in females). Based on a comprehensive assessment of the available toxicology data and the CMV-specific target, letermovir is not expected to be carcinogenic in humans.

Impairment of Fertility

In a fertility and early embryonic development study in rats, no effects of letermovir on female fertility were observed at letermovir exposures (AUC) approximately 5 times higher than human exposure at the RHD.

In male rat fertility studies, decreased fertility associated with irreversible testicular toxicity was observed at ≥180 mg/kg/day (greater than or equal to 3 times the human exposure at the RHD). No fertility or testicular effects were observed at dose levels resulting in letermovir exposures (AUC) similar to human exposure at the RHD [*see Clinical Pharmacology (10.3.2)*].

10.3.2 Animal Toxicology and/or Pharmacology

Testicular toxicity in rats observed at ≥180 mg/kg/day (greater than or equal to 3 times the human exposure at the RHD) was characterized by decreased testis weight, bilateral seminiferous tubular degeneration, decreased sperm count and motility, and resultant decreased male rat fertility. Male reproductive system toxicities were not observed in either a monkey testicular toxicity study up to 240 mg/kg/day (approximately 2 times higher than human exposure at the RHD), or a general toxicology study in mice up to 250 mg/kg/day (approximately 3 times higher than human exposure at the RHD).

11 Pharmacokinetics

The pharmacokinetic properties of letermovir are displayed in Table 5.

Table 5: Absorption, Distribution, Metabolism, Elimination (ADME), and Pharmacokinetic Properties of PREVYMIS*

Pharmacokinetics in HSCT Recipients	
Treatment Regimen 480 mg oral once daily, no cyclosporine 480 mg IV once daily, no cyclosporine 240 mg oral once daily, with cyclosporine 240 mg IV once daily, with cyclosporine	Steady-state median (90% prediction interval) AUC (ng•hr/mL) of PREVYMIS 34,400 (16,900, 73,700) 100,000 (65,300, 148,000) 60,800 (28,700, 122,000) 70,300 (46,200, 106,000)
Pharmacokinetics in Kidney Transplant Recipients	
Treatment Regimen 480 mg oral once daily, no cyclosporine 240 mg oral once daily, with cyclosporine	Steady-state median (90% prediction interval) AUC (ng•hr/mL) of PREVYMIS 62,200 (28,900, 145,000) 57,700 (26,900, 135,000)
Pharmacokinetics in Healthy Subjects	
Treatment Regimen 480 mg oral once daily	Steady-state geometric mean AUC and Cmax of PREVYMIS Cmax: 13,000 ng/mL AUC: 71,500 ng•hr/mL
Dose proportionality	Greater than dose proportional following single and multiple oral or IV doses of PREVYMIS 240 mg and 480 mg
Accumulation ratio†	Cmax: 1.03 AUC: 1.22
Time to steady-state	9-10 days
Absorption	
Bioavailability	Healthy subjects administered PREVYMIS without cyclosporine: 94% at an oral dose range of 240 mg to 480 mg HSCT recipients administered PREVYMIS without cyclosporine: 35% with 480 mg oral once daily HSCT recipients administered PREVYMIS with cyclosporine: 85% with 240 mg oral once daily Kidney transplant recipients administered PREVYMIS without cyclosporine: 60% with 480 mg oral once daily
Median Tmax (hr)	1.5 to 3.0 hr
Effect of food (relative to fasting)‡	AUC: 99.63% [84.27% - 117.80%] Cmax: 129.82% [104.35% -161.50%]
Distribution	
Mean steady-state volume of distribution	45.5L following IV administration in HSCT recipients
% In vitro bound to human plasma proteins	99% across the concentration range of 0.2 to 50 mg/L

In vitro blood-to plasma ratio	0.56 across the concentration range of 0.1 to 10 mg/L
Metabolism	
In vitro metabolism	UGT1A1/1A3 (minor)
Drug-related component in plasma	97% unchanged parent No major metabolites detected in plasma
Elimination	
Route of elimination	Hepatic uptake (OATP1B1/3)
Mean terminal t1/2 (hr)	12 hrs after dosing of PREVYMIS 480 mg IV once daily
% of dose excreted in feces[§]	93%
% of dose excreted in urine[§]	<2%
% of unchanged drug excreted in feces[§]	70%
[*] Values were obtained in studies of healthy subjects unless otherwise indicated. [†] Based on geometric mean data. [‡] Values refer to geometric mean ratio [fed/fasted] percentage and 90% confidence interval back transformed from linear mixed-effects model performed on natural log-transformed values. The meal administered was a standard high fat and high calorie meal (33 grams protein, 65 grams carbohydrates, 58 grams fat; 920 total calories). [§] Single oral administration of radiolabeled letermovir in mass balance study.	

Specific Populations

Pediatric Population

The pharmacokinetics of letermovir in patients less than 18 years of age have not been evaluated.

Age, Gender, Race, and Weight

Age (18 to 82 years), gender, race (White vs. non-White), and body weight (up to 100 kg) did not have a clinically significant effect on the pharmacokinetics of letermovir.

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/1.73m^2) and severe (eGFR less than 30 mL/min/1.73m^2) renal impairment, respectively, compared to healthy subjects.

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 (CLCr greater than or equal to 60 to less than 90 mL/min), moderate (CLCr greater than or equal to 30 to less than 60 mL/min) and severe (CLCr greater than or equal to 15 to less than 30 mL/min) renal impairment, respectively, compared to subjects with CLCr greater than or equal to 90 mL/min.

Intravenous Formulation

Hydroxypropyl betadex present in the intravenous letermovir formulation is mainly eliminated by glomerular filtration. Decreased elimination of hydroxypropyl betadex has been reported in the literature in patients with severe renal impairment.

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.

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 6 and Table 7)*.

In vitro results indicate that letermovir is a substrate of drug metabolizing enzymes CYP3A, CYP2D6, UGT1A1, and UGT1A3, and transporters OATP1B1/3 and P-gp. Oxidative metabolism is considered to be a minor elimination pathway based on *in vivo* human data. Inhibitors of OATP1B1/3 may result in increases in letermovir plasma concentrations. Changes in letermovir plasma concentrations due to inhibition of P-gp/BCRP by itraconazole were not clinically relevant. Changes in letermovir plasma concentrations due to inhibition of UGTs are not anticipated to be clinically relevant. 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 Interactions (7.1), Table 1, and Table 6]*.

Based on *in vitro* studies, the metabolism of letermovir is not mediated by CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2E1, CYP4A11, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B15, or UGT2B17. The transport of letermovir is not mediated by OATP2B1, OCT1, OAT1, BCRP, or MRP2 *in vitro*.

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 7). Based on these results, co-administration of PREVYMIS with CYP3A substrates may increase the plasma concentrations of the CYP3A substrates *[see Contraindications (4), Warnings and Precautions (5.1), Interactions (7.2, 7.3)*, and Table 1*]*. Letermovir is a reversible inhibitor of CYP2C8 *in vitro*. When co-administered with PREVYMIS, plasma concentrations of CYP2C8 substrates are predicted to be increased *[see Table 1 in Interactions (7.3)].* 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 in Interactions (7.3)].* 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 in Interactions (7.3)].* 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 7). The effect of letermovir on BCRP, BSEP, and MRP2 substrates was not evaluated in clinical studies; the clinical relevance is unknown.

Based on *in vitro* results letermovir is not an inhibitor of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, UGT1A4, UGT1A6, UGT1A9, or UGT2B7 and is not an inducer of CYP1A2. Letermovir is not an inhibitor of OATP2B1, OCT1, OCT2, or OAT1 *in vitro*.

Table 6: Drug Interactions: Changes in Pharmacokinetics of Letermovir in the Presence of Co-administered Drug

Co- administered Drug	**Regimen of Co-administered Drug**	**Letermovir Regimen**	**Geometric Mean Ratio [90% CI] of Letermovir PK with/without Co-administered Drug (No Effect=1.00)**		
			AUC	**Cmax**	**C24hr***
Antifungals					
fluconazole	400 mg single dose PO	480 mg single dose PO	1.11 (1.01, 1.23)	1.06 (0.93, 1.21)	1.28 (1.15, 1.43)
itraconazole	200 mg once daily PO	480 mg once daily PO	1.33 (1.17, 1.51)	1.21 (1.05, 1.39)	1.90 (1.58, 2.28)
Antimycobacterials					

rifampin	600 mg single dose PO	480 mg single dose PO	2.03 (1.84, 2.26)	1.59 (1.46, 1.74)	2.01 (1.59, 2.54)
	600 mg single dose IV	480 mg single dose PO	1.58 (1.38, 1.81)	1.37 (1.16, 1.61)	0.78 (0.65, 0.93)
	600 mg once daily PO	480 mg once daily PO	0.81 (0.67, 0.98)	1.01 (0.79, 1.28)	0.14 (0.11, 0.19)
	600 mg once daily PO (24 hours after rifampin)[†]	480 mg once daily PO	0.15 (0.13, 0.17)	0.27 (0.22, 0.31)	0.09 (0.06, 0.12)
Immunosuppressants					
cyclosporine	200 mg single dose PO	240 mg once daily PO	2.11 (1.97, 2.26)	1.48 (1.33, 1.65)	2.06 (1.81, 2.35)
mycophenolate mofetil	1 g single dose PO	480 mg once daily PO	1.18 (1.04, 1.32)	1.11 (0.92, 1.34)	1.39 (1.12, 1.74)
tacrolimus	5 mg single dose PO	80 mg twice daily PO	1.02 (0.97, 1.07)	0.92 (0.84, 1.00)	1.02 (0.93, 1.12)

Abbreviations: PO= oral

* C12hr for tacrolimus

[†]These data are the effect of rifampin on letermovir 24 hours after final rifampin dose.

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

Co- administered Drug	**Regimen of Co-administered Drug**	**Letermovir Regimen**	**Geometric Mean Ratio [90% CI] of Co-administered Drug PK with/without Letermovir (No Effect=1.00)**		
			AUC	**Cmax**	**C24hr***
CYP3A Substrates					
midazolam	1 mg single dose IV	240 mg once daily PO	1.47 (1.37, 1.58)	1.05 (0.94, 1.17)	2.74 (2.16, 3.49)
	2 mg single dose PO	240 mg once daily PO	2.25 (2.04, 2.48)	1.72 (1.55, 1.92)	Not available
P-gp Substrates					
digoxin	0.5 mg single dose PO	240 mg twice daily PO	0.88 (0.80, 0.96)	0.75 (0.63, 0.89)	0.90 (0.84, 0.96)
Immunosuppressants					
cyclosporine	50 mg single dose PO	240 mg once daily PO	1.66 (1.51, 1.82)	1.08 (0.97, 1.19)	2.19 (1.80, 2.66)
mycophenolate mofetil	1 g single dose PO	480 mg once daily PO	1.08 (0.97, 1.20)	0.96 (0.82, 1.12)	1.04 (0.86, 1.27)
tacrolimus	5 mg single dose PO	480 mg once daily PO	2.42 (2.04, 2.88)	1.57 (1.32, 1.86)	2.53 (2.12, 3.03)

sirolimus	2 mg single dose PO	480 mg once daily PO	3.40 (3.01, 3.85)	2.76 (2.48, 3.06)	3.15 (2.80, 3.55)
Antifungals and Antivirals					
acyclovir	400 mg single dose PO	480 mg once daily PO	1.02 (0.87, 1.2)	0.82 (0.71, 0.93)	1.13 (0.94, 1.36)
fluconazole	400 mg single dose PO	480 mg single dose PO	1.03 (0.99, 1.08)	0.95 (0.92, 0.99)	1.04 (1.00, 1.08)
itraconazole	200 mg once daily PO	480 mg once daily PO	0.76 (0.71, 0.81)	0.84 (0.76, 0.92)	0.67 (0.61, 0.73)
posaconazole	300 mg single dose PO	480 mg once daily PO	0.98 (0.82, 1.17)	1.11 (0.95, 1.29)	1.10 (0.94, 1.30)
voriconazole	200 mg twice daily PO	480 mg once daily PO	0.56 (0.51, 0.62)	0.61 (0.53, 0.71)	0.49 (0.42, 0.57)
HMG-CoA Reductase Inhibitors					
atorvastatin	20 mg single dose PO	480 mg once daily PO	3.29 (2.84, 3.82)	2.17 (1.76, 2.67)	3.62 (2.87, 4.55)
Oral Contraceptives					
ethinyl estradiol (EE) /levonorgestrel (LNG)	0.03 mg EE single dose PO	480 mg once daily PO	1.42 (1.32, 1.52)	0.89 (0.83, 0.96)	1.57 (1.45, 1.70)
	0.15 mg LNG single dose PO		1.36 (1.30, 1.43)	0.95 (0.86, 1.04)	1.38 (1.32, 1.46)
Abbreviations: PO=oral * C12hr reported for voriconazole.					

12 Clinical Studies

12.1 Adult CMV-seropositive Recipients [R+] of an Allogeneic Hematopoietic 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, NCT02137772) in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). Subjects were randomized (2:1) to receive either PREVYMIS at a dose of 480 mg once daily adjusted to 240 mg when co-administered with cyclosporine, or placebo. Randomization was stratified by investigational site and risk level for CMV reactivation at the time of study entry. Study drug was initiated after HSCT (at any time from Day 0 to Day 28 post-HSCT) and continued through Week 14 post-HSCT. Study drug was administered either orally or intravenously; the dose of PREVYMIS was the same regardless of the route of administration. Subjects received CMV DNA monitoring weekly until post-HSCT Week 14 and then bi-weekly until post-HSCT Week 24, with initiation of standard-of-care CMV pre-emptive therapy if CMV viremia was considered clinically significant. Subjects had continued follow-up through Week 48 post-HSCT.

Among the 565 treated subjects, 70 subjects were found to have CMV viremia prior to study drug initiation and were therefore excluded from the efficacy analyses. The efficacy population consisted of 325 subjects who received PREVYMIS (including 91 subjects who received at least one IV dose) and 170 who received placebo (including 41 subjects who received at least one IV dose). The IV formulation of PREVYMIS was used at investigators' discretion in subjects who were unable to take oral therapy (e.g., unable to tolerate oral intake). The median time to starting study drug was 8 days after transplantation. Thirty-four percent (34%) of subjects were engrafted at baseline. The median age was 55 years (range: 18 to 76 years); 57% were male; 84% were White; 9% were Asian; 2% were Black or African American; and 7% were Hispanic or Latino.

At baseline, 30% of all subjects had one or more of the following factors associated with increased risk for CMV reactivation (high risk stratum): Human Leukocyte Antigen (HLA)-related 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 70% of subjects did not meet any of these high risk stratum criteria and were therefore included in the low risk stratum. Additionally, 48% of subjects received a myeloablative regimen, 51% were receiving cyclosporine, and 43% were receiving tacrolimus. The most common primary reasons for transplant were acute myeloid leukemia (38%), myelodysplastic syndrome (16%), and lymphoma (12%).

Clinically Significant CMV Infection

The primary efficacy endpoint of Trial P001 was the incidence of clinically significant CMV infection through Week 24 post-HSCT (prophylaxis failure). 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 viremia (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 protocol-specified guidance for CMV DNA thresholds for the initiation of PET during the treatment period was ≥ 150 copies/mL or > 300 copies/mL for subjects in the high and low risk strata, respectively. From Week 14 through Week 24, the threshold was >300 copies/mL for both high and low risk strata subjects. The Non-Completer=Failure (NC=F) approach was used, where subjects who discontinued from the trial prior to Week 24 post-HSCT or had a missing outcome at Week 24 post-HSCT were counted as failures.

Efficacy results from Trial P001 are shown in Table 8.

Table 8: Trial P001 Efficacy Results in HSCT Recipients (NC=F Approach, FAS Population) Through Week 24

Parameter	Letermovir (N=325)	Placebo (N=170)
Proportion of subjects who failed prophylaxis	**38%**	**61%**
Reasons for failures*		
Clinically significant CMV infection by Week 24†	18%	42%
Initiation of PET based on documented CMV viremia	16%	40%
CMV end-organ disease	2%	2%
Discontinued from study before Week 24‡	17%	16%
Missing outcome in Week 24 visit window	3%	3%
Stratum-adjusted treatment difference (Letermovir-Placebo)§		
Difference (95% CI)	-23.5 (-32.5, -14.6)¶	

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

† Through Week 14, 8% of subjects in the PREVYMIS group and 39% of subjects in the placebo group experienced clinically significant CMV infection.

‡ Reasons for discontinuation included adverse event, death, lost to follow-up, physician decision, and withdrawal by subject.

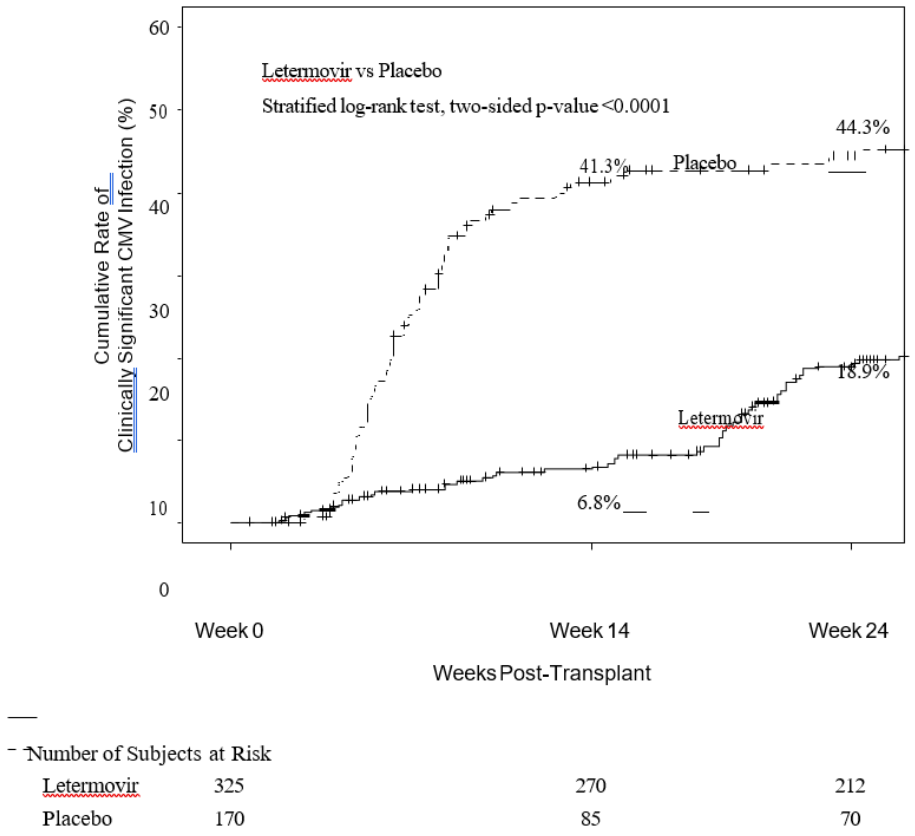
§ 95% CI and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk).

¶ p-value <0.0001.

Note: FAS=Full analysis set; FAS includes randomized 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.

Efficacy results were consistent across high and low risk strata for CMV reactivation. The time to clinically significant CMV infection is shown in Figure 1.

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

Post-hoc analysis demonstrated that among PREVYMIS-treated subjects, inclusion in the high risk stratum for CMV reactivation at baseline, occurrence of GVHD, and steroid use at any time after randomization may be associated with the development of clinically significant CMV infection between Week 14 and Week 24 post-HSCT.

Mortality

The Kaplan-Meier event rate for all-cause mortality in the letermovir vs. placebo groups was 12% vs. 17% at Week 24 post-HSCT, and 24% vs. 28% at Week 48 post-HSCT.

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, NCT03930615) in adult CMV-seropositive recipients [R+] of an allogeneic HSCT. Eligible subjects who completed PREVYMIS prophylaxis through ~100 days post-HSCT were randomized (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.

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. The most common reasons for transplant were acute myeloid leukemia (42%), acute lymphocytic leukemia (15%), and myelodysplastic syndrome (11%).

Clinically Significant CMV Infection

The primary efficacy endpoint of Trial 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 viremia 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 viremia were counted as failures.

Efficacy results from Trial P040 are shown in Table 9. Efficacy was consistent across subgroups based on participant characteristics (age, gender, race) and risk factors for late CMV infection and disease.

Table 9: Trial 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)	Placebo (~100 days PREVYMIS) (N=74)
Failures*	**2.8%**	**18.9%**
Clinically significant CMV infection through Week 28[†]	1.4%	17.6%
Initiation of PET based on documented CMV viremia	0.7%	14.9%
CMV end-organ disease	0.7%	2.7%
Discontinued from study with CMV viremia before Week 28	1.4%	1.4%
Stratum-adjusted treatment difference (PREVYMIS (~200 days PREVYMIS)-Placebo (~100 days PREVYMIS))[‡]		
Difference (95% CI)	-16.1 (-25.8, -6.5)[§]	

[*] 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 viremia and the clinical condition of the subject.

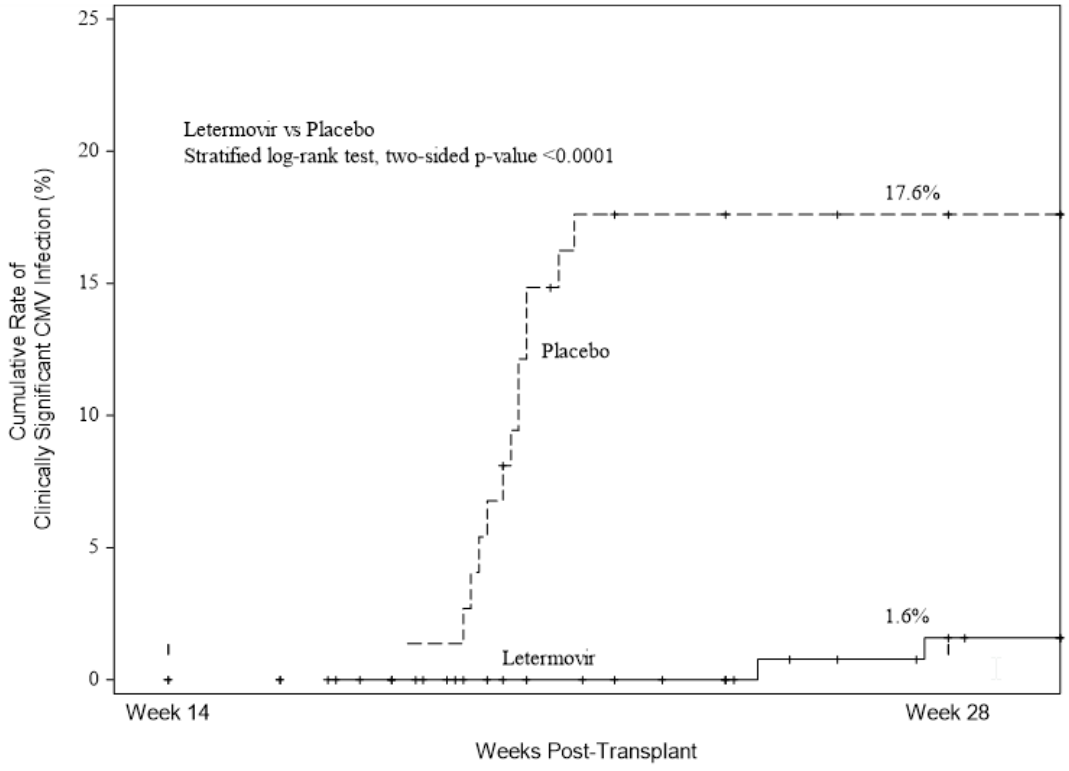
[‡] 95% CIs and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (haploidentical donor yes or no). A one-sided p-value ≤0.0249 was used for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

[§] p-value = 0.0005

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 viremia from Week 14 (~100 days) through Week 28 (~200 days) post-HSCT.

The time to clinically significant CMV infection is shown in Figure 2.

Figure 2: Trial 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

12.2 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 non-inferiority Phase 3 trial (P002, NCT03443869) in adult kidney transplant recipients at high risk [D+/R-]. Subjects were randomized (1:1) to receive either PREVYMIS or valganciclovir. 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; the dose of PREVYMIS was the same regardless of the route of administration. 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%).

CMV Disease

The primary efficacy endpoint of Trial 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.

Efficacy results from Trial P002 are shown in Table 10.

Table 10: Trial P002 Efficacy Results in Kidney Transplant Recipients (OF Approach, FAS Population)

Parameter	PREVYMIS (N=289)	Valganciclovir (N=297)
CMV disease* through Week 52	**10%**	**12%**
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 randomized to the PREVYMIS group were given acyclovir for herpes simplex virus (HSV) and varicella zoster virus (VZV) prophylaxis. Subjects randomized to the valganciclovir group were given a placebo to acyclovir.

Efficacy was comparable across all subgroups, including the use/nonuse of highly cytolytic, anti-lymphocyte immunotherapy during induction.

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

13 How Supplied/Storage and Handling

13.1 How supplied

Tablets:

Each PREVYMIS 240 mg tablet is a yellow oval tablet; each tablet is debossed with “591” on one side and corporate logo on the other side. Each PREVYMIS 480 mg tablet is a pink oval, bi-convex tablet debossed with “595” on one side and corporate logo on the other side.

Tablets are packaged into a carton containing 28 tablets.

Injection:

PREVYMIS is supplied as a sterile, clear solution for intravenous use of 240 mg (12 mL per vial) or 480 mg (24 mL per vial) that may contain a few product-related small translucent or white particles. The final solutions for infusion are obtained by dilution with 0.9% Sodium Chloride Injection or 5% Dextrose Injection.

The single dose vials are supplied in cartons that contain a 240 mg single-dose vial or a 480 mg single-dose vial.

13.2 Shelf Life

Please refer to outer carton.

13.3 Storage Condition

Tablets:

Store PREVYMIS tablets below 30°C.

Injection:

Store PREVYMIS injection vials below 25°C.

13.4 Special precautions for storage

Tablets:

Store PREVYMIS tablets in the original package until use.

Injection:

Store in the original carton to protect from exposure to light.

14 Patient Counseling Information

Drug Interactions

Inform patients that PREVYMIS may interact with some drugs; therefore, advise patients to report the use of any prescription, non-prescription medication, or herbal products to their healthcare provider *[see Dosage and Administration (3.3.1), Contraindications (4), Warnings and Precautions (5.1), and Interactions (7)]*.

Administration

Inform patients that it is important not to miss doses and to take PREVYMIS for the duration that is recommended by the healthcare provider. Instruct patients closely that if they miss a dose of PREVYMIS, they should take it in the day as soon as they remember; they should not skip the dose of the day. If they do not remember until it is time for the next dose, instruct them to skip the missed dose, go back to the regular schedule, and address the importance of taking drug regularly to the patients. Instruct patients not to double their next dose or take more than the prescribed dose.

Storage

Advise patients to store PREVYMIS tablets in the original package until use *[see How Supplied/Storage and Handling (13)]*.

15 References

uspi-mk8228-mf-1711r000

CCDS-MK8228-MF-112022

MSD-000026076-TW-20240315

Prevymis F.C. Tablets 240mg and 480mg

Manufacturing Site: MSD International GmbH

Address: Ballydine, Kilsheelan, Clonmel, Co. Tipperary, Ireland

Primary and Secondary Packaging Site: Organon Heist bv

Address: Industriepark 30, 2220 Heist-op-den-Berg, Belgium

Prevymis Concentrate for Solution for Infusion 20mg/mL

Manufacturing Site: MSD International GmbH T/A MSD Ireland (Carlow)

Address: Dublin Road, Carlow Co. Carlow, Ireland

Packaging Site: Organon Heist bv

Address: Industriepark 30, 2220 Heist-op-den-Berg, Belgium

Marketing Authorization Holder: Merck Sharp & Dohme (I.A.) LLC, Taiwan Branch

Address: 12F., No.106, Sec. 5, Xinyi Dist., Xinyi Rd., Taipei City, Taiwan