PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

℞ PREVYMIS™

letermovir tablets
Tablets, 240 mg and 480 mg, oral

letermovir for injection
Solution for injection, 20 mg/mL, 240 mg/vial and 480 mg/vial, intravenous

Antiviral Agent

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RECENT MAJOR LABEL CHANGES

Not applicable

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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

1.1 Pediatrics (< 18 years of age)

Safety and efficacy of PREVYMIS™ have not been established in pediatric patients less than 18 years of age.

1.2 Geriatrics (≥ 65 years of age)

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

2 CONTRAINDICATIONS

PREVYMIS™ is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

Pimozide
Concomitant administration of PREVYMIS™ may result in increased concentrations of pimozide due to inhibition of cytochrome P450 3A (CYP3A) by letermovir, leading to QT prolongation and torsades de pointes (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Ergot Alkaloids
Concomitant administration of PREVYMIS™ may result in increased concentrations of ergot alkaloids (ergotamine and dihydroergotamine) due to inhibition of CYP3A by letermovir, which may lead to ergotism (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

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

PREVYMIS™ Injection

- Do not administer as an IV bolus injection.
- Administer by intravenous (IV) infusion upon dilution via a peripheral catheter or central venous line over approximately 60 minutes.

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

3.2 Recommended Dose and Dosage Adjustment

Recommended Dosage

Adults:

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

If PREVYMIS™ is co-administered with cyclosporine, the dosage of PREVYMIS™ should be decreased to 240 mg once daily (see Dosage Adjustment in Adults section below)**.**

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.

Pediatrics (< 18 years of age):
Safety and efficacy of PREVYMIS™ have not been established in pediatric patients less than 18 years of age.

Geriatrics (≥ 65 years of age):
No dose adjustment of PREVYMIS™ is required based on age (see ACTION and CLINICAL PHARMACOLOGY, Pharmacokinetics).

Dosage Adjustment in Adults
If PREVYMIS™ is co-administered with cyclosporine, the dosage of PREVYMIS™ should be decreased to 240 mg once daily (see DOSAGE AND ADMINISTRATION, Reconstitution, DRUG INTERACTIONS and ACTION and CLINICAL PHARMACOLOGY, Pharmacokinetics and Table 3).

- 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 temporarily interrupted due to high cyclosporine levels, no dose adjustment of PREVYMIS™ is needed.

Renal Impairment
No dose adjustment of PREVYMIS™ is required based on renal impairment (see DOSAGE AND ADMNISTRATION, Hepatic Impairment**,** WARNINGS AND PRECAUTIONS, Renal Impairment and ACTION and CLINICAL PHARMACOLOGY, Pharmacokinetics).

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.

Combined Renal and Hepatic Impairment
PREVYMIS™ is not recommended in patients with moderate hepatic impairment combined with moderate or severe renal impairment (CrCl less than 50 mL/min) (see WARNINGS AND PRECAUTIONS, Hepatic Impairment and ACTION and CLINICAL PHARMACOLOGY, Pharmacokinetics).

3.3 Administration

PREVYMIS™ injection 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 only. Discard any unused portion.

- Administer as an IV infusion upon dilution only. Do not administer as an IV push or bolus.
- After dilution, administer PREVYMIS™ via IV infusion via peripheral or central venous catheter using a total time of approximately 60 minutes. Administer the entire contents of the IV bag.

Preparation

- PREVYMIS™ must be diluted prior to IV use.
- Inspect vial contents for discoloration and particulate matter prior to dilution. PREVYMIS™ injection is a clear colorless solution. Do not use the vial if the solution is discolored or contains visible particles.
- Do not shake PREVYMIS™ vial.

3.4 Reconstitution

- Add one single-dose vial of PREVYMIS™ injection to a 250 mL pre-filled IV bag containing either 0.9% sodium chloride injection or 5% dextrose injection 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.

Storage of Diluted Solution

- The diluted solution can be stored for up to 24 hours at room temperature or up to 48 hours under refrigeration at 2°C to 8°C.

- This time includes storage of the diluted solution in the IV bag through the duration of infusion.

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

Compatible Diluents
PREVYMIS™ injection is compatible with 0.9% sodium chloride injection and 5% dextrose injection.

Compatible Drug Products
A study was conducted to evaluate physical compatibility of PREVYMIS™ injection 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 IV 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
- Anti-thymocyte globulin
- Caspofungin
- Daptomycin
- Fentanyl citrate
- Fluconazole
- Furosemide
- Humulin* R (human insulin)
- Magnesium sulfate
- Methotrexate
- Micafungin

† These injectable drug products are available in Canada

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
- Ceftriaxone sodium
- Famotidine
- Folic acid
- Ganciclovir sodium
- Hydrocortisone sodium succinate
- Morphine sulfate
- Norepinephrine bitartrate
- Pantoprazole sodium

- Potassium chloride
- Potassium phosphate
- Tacrolimus
- Telavancin
- Tigecycline

† These injectable drug products are available in Canada

Amphotericin B (lipid complex) is compatible with PREVYMIS™. However, Amphotericin B (liposomal) is incompatible (see below DOSAGE AND ADMINISTRATION, Incompatible Drug Products and Other Materials Used for Intravenous Administration).

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 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:
Diethylhexyl-phthalate (DEHP), tris (2-ethylhexyl) trimellitate (TOTM), butyl benzyl phthalate (BBP)

Catheters:
Radiopaque polyurethane

Incompatible Drug Products and Other Materials Used for Intravenous Administration

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

Incompatible IV Bags and Infusion Set Materials
PREVYMIS™ injection is incompatible with polyurethane-containing IV administration set tubing.

3.5 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

4 OVERDOSAGE

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.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

PREVYMIS™ contains letermovir, an anti-CMV agent, and is administered orally or by IV infusion.

Table 1 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablet 240 mg, 480 mg	Colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and povidone 25. Film-coating: hypromellose 2910, iron oxide yellow, and (only for 480 mg tablets) iron oxide red, lactose monohydrate, titanium dioxide and triacetin. Carnauba wax is added as a polishing agent.
Intravenous infusion	Solution for Injection 20 mg / mL	Clear, preservative-free sterile solution in single-dose vials of either 240 mg or 480 mg per vial. Each 1 mL of solution contains 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.

Tablet:
PREVYMIS™ 240 mg tablet is a yellow oval tablet. Each tablet is debossed with “591” on one side and Merck logo on the other side. The 240 mg tablets are packaged in aluminum foil blister and lidding in cartons of 28 tablets.

PREVYMIS™ 480 mg tablet is a pink oval, bi-convex tablet. Each tablet is debossed with “595” on one side and Merck logo on the other side. The 480 mg tablets are packaged in aluminum foil blister and lidding in cartons of 28 tablets.

Solution for Injection:
PREVYMIS™ for injection 240 mg/12 mL (20 mg/mL) is supplied in a single-dose vial.

PREVYMIS™ for injection 480 mg/24 mL (20 mg/mL) is supplied in a single-dose vial.

6 WARNINGS AND PRECAUTIONS

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 3 for steps to prevent or manage these known or potentially significant drug interactions, including dosing recommendations (see CONTRAINDICATIONS and DRUG INTERACTIONS, Overview and Drug-Drug Interactions). Consider the potential for drug interactions prior to and during PREVYMIS™ therapy; review concomitant medications during PREVYMIS™ therapy; and monitor for the adverse reactions associated with the concomitant drugs.

PREVYMIS™ should be used with caution with drugs that are CYP3A substrates with narrow therapeutic ranges (e.g. alfentanil, fentanyl, and quinidine[1]) 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 3 and DRUG INTERACTIONS, Overview and Drug-Drug Interactions).

Co-administration of PREVYMIS™ may result in increases in the plasma concentrations of cyclosporine, tacrolimus, and sirolimus. Close monitoring and/or dose adjustment of cyclosporine, tacrolimus, and sirolimus is recommended when co-administered with PREVYMIS™.

6.1 Special Populations

6.1.1 Pregnant Women

No human data are available to establish whether or not PREVYMIS™ poses a risk to pregnancy outcomes, therefore, the potential risk to humans is unknown. PREVYMIS™ should not be used in pregnancy unless benefit outweighs the risk.

Embryofetal toxicity was observed in rats and rabbits at maternally toxic systemic exposures based on AUC of approximately 11- and 2-fold, respectively, at the recommended human dose (RHD). In the rat pre-and postnatal development study, no developmental toxicity was observed up to the highest maternal systemic exposure based on AUC (approximately 2-fold the AUC at the RHD).

In pregnant rats, letermovir was able to cross the placenta (see ACTION and CLINICAL PHARMACOLOGY, Pharmokinetics**).**

Females and Males of Reproductive Potential

Infertility
There were no effects on female fertility in rats. Impairment of fertility was observed in male rats, but not in male mice or male monkeys (see NON-CLINICAL TOXICOLOGY). Testicular toxicity in rats appears to be species-specific, 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 ADVERSE REACTIONS).

6.1.2 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.

6.1.3 Pediatrics (< 18 years of age)

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

6.1.4 Hepatic Impairment

Exposure to PREVYMIS™ is increased 1.6- to 3.8 -fold in subjects with moderate and severe 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 DOSAGE AND ADMINISTRATION and ACTION and CLINICAL PHARMACOLOGY, Pharmacokinetics).

6.1.5 Renal Impairment

Exposure to PREVYMIS™ is increased 1.4- to 1.9-fold in subjects with moderate and severe renal impairment. No dose adjustment of PREVYMIS™ is required based on renal impairment (see DOSAGE AND ADMINISTRATION, Renal Impairment, Hepatic Impairment, WARNINGS AND PRECAUTIONS, Hepatic Impairment and ACTION and CLINICAL PHARMACOLOGY, Pharmacokinetics). 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™ injection, accumulation of the IV vehicle, hydroxypropyl betadex, could occur (see NON-CLINICAL TOXICOLOGY). Serum creatinine levels should be closely monitored in these patients.

6.1.6 Combined Renal and Hepatic Impairment

PREVYMIS™ is not recommended in patients with moderate hepatic impairment combined with moderate or severe renal impairment (see DOSAGE AND ADMINISTRATION and ACTION and

CLINICAL PHARMACOLOGY, Pharmacokinetics).

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

The safety summary for PREVYMIS™ was based on data from a randomized, placebo-controlled Phase 3 clinical trial P001 in which CMV seropositive HSCT recipients received letermovir or placebo.

The most commonly reported adverse reactions in subjects treated with PREVYMIS™ through Week 24 post-transplant were nausea, diarrhea, and vomiting.

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adult CMV-seropositive Recipients [R+] of an Allogeneic HSCT
The safety of PREVYMIS™ was evaluated in a Phase 3 randomized, double-blind, placebo-controlled trial (P001) through Week 14 post-transplant and were followed for safety through Week 24 post-transplant (see CLINICAL TRIALS).

The most commonly reported adverse reactions occurring in at least 1% of subjects in the PREVYMIS™ group through Week 24 post-transplant and at a frequency greater than placebo were: nausea, diarrhea, and vomiting (see Table 2).

Table 2 - P001 Adverse Reactions Reported in ≥1% HSCT Recipients in the PREVYMIS™ Group and at a Frequency Greater than Placebo Through Week 24 Post-Transplant

Adverse Reaction	PREVYMIS™ (N=373)	Placebo (N=192)
	n (%)	n (%)
Gastrointestinal		
nausea	27 (7.2)	7 (3.6)
diarrhea	9 (2.4)	2 (1.0)
vomiting	7 (1.9)	2 (1.0)

Serious adverse reactions through week 24 post-transplant were reported in 6 (1.1%) subjects with 3 (0.8%) in the PREVYMIS™ group and 3 (1.6%) in the placebo group. The reported serious adverse reactions, which had a temporal association but no other plausible causal relationship to study treatment, were pancytopenia, thrombocytopenia, and delayed engraftment in the letermovir group and Bowen's disease, mental status changes, and acute kidney injury in the placebo group.

Cardiac Adverse Events:
Cardiac adverse events were more common 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 3.5% of PREVYMIS™ subjects and in 1% of placebo subjects). These adverse events were mostly considered mild or moderate in severity.

Hypersensitivity was reported with PREVYMIS™ in one subject.

Overall, similar proportions of subjects in each group discontinued study medication due to an adverse reaction (4.8% PREVYMIS™ vs. 3.6% placebo). The most frequently reported adverse reactions that led to discontinuation of PREVYMIS™ were nausea (1.6%), vomiting (0.8%), and abdominal pain (0.5%).

7.3 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Overall, the percentage of subjects with potentially clinically significant changes in laboratory values (e.g. hematology, 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 (defined as absolute neutrophil count ≥ 500/mm^3 on 3 consecutive days after transplantation) between the PREVYMIS™ and placebo groups.

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

7.4 Clinical Trial Adverse Reactions (Pediatrics)

The clinical trials have not been conducted in a pediatric population.

8 DRUG INTERACTIONS

8.1 Serious Drug Interactions Box

Serious Drug Interactions

Pimozide
Pimozide is contraindicated with PREVYMIS™. Concomitant administration of PREVYMIS™ may result in increased concentrations of pimozide due to inhibition of cytochrome P450 3A (CYP3A) by letermovir, leading to QT prolongation and torsades de pointes (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Ergot Alkaloids
Ergot Alkaloids are contraindicated with PREVYMIS™. 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 CONTRAINDICATIONS WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

8.2 Overview

Effect of Other Drugs on PREVYMIS™
Letermovir is a substrate of organic anion-transporting polypeptide 1B1/3 (OATP1B1/3) transporters. 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 cyclosporine (a potent OATP1B1/3 inhibitor), the recommended dose of PREVYMIS™ is 240 mg once daily (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, ACTION and CLINICAL PHARMACOLOGY, Pharmacokinetics, and Table 3).

Effect of PREVYMIS™ on Other Drugs
Letermovir is a moderate inhibitor of CYP3A, based on clinical studies using midazolam as probe. 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. PREVYMIS™ is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening reactions. PREVYMIS™ should be used with caution with other CYP3A substrates and adverse reactions to these drugs monitored as appropriate (**see** CONTRAINDICATIONS, WARNINGS AND PRECAUTION**S**, and Table 3).

Letermovir is an inhibitor of OATP1B1/3 transporters BCRP, BSEP, MRP2, and UGT1A1. 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 3).

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 product monograph for cyclosporine for information on drug interactions with cyclosporine.

8.3 Drug-Drug Interactions

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 3 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 WARNINGS AND PRECAUTIONS and ACTION and CLINICAL PHARMACOLOGY, Pharmacokinetics).

Table 3 - Potentially Significant Drug Interactions: Alteration in Dose May Be Recommended Based on Results from Drug Interaction Studies or Predicted Interactions[β] (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 Comment
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™. When PREVYMIS™ is co-administered with cyclosporine, use of amiodarone is not recommended.
Antidiabetic Agents		
Examples: glyburide, repaglinide, rosiglitazone	↑glyburide ↑repaglinide ↑rosiglitazone	PREVYMIS™ may increase the plasma concentrations of glyburide, repaglinide, and rosiglitazone. Frequent monitoring of glucose concentrations is recommended during co-administration of glyburide, repaglinide, and rosiglitazone[§]. When PREVYMIS™ is co-administered with cyclosporine, use of repaglinide is not 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[§].
HMG-CoA Reductase Inhibitors		
atorvastatin[‡]	↑ atorvastatin	Co-administration of PREVYMIS™ with atorvastatin increases plasma concentrations of atorvastatin. The dose of atorvastatin should not exceed 20 mg daily when co-administered with PREVYMIS™[§]. Closely monitor patients for adverse reactions such as myopathy. When PREVYMIS™ is co-administered with cyclosporine, use of atorvastatin is not recommended.
simvastatin	↑ simvastatin	Concomitant use with PREVYMIS™ is not recommended. When PREVYMIS™ is co-administered with cyclosporine, use of simvastatin is contraindicated.
fluvastatin, pravastatin, rosuvastatin	↑ fluvastatin, pravastatin, rosuvastatin	When PREVYMIS™ is co-administered with these statins, a statin dosage reduction may be necessary[§]. Closely monitor patients for adverse reactions such as myopathy. When PREVYMIS™ is co-administered with cyclosporine, refer to the statin product monograph for specific statin dosing recommendations[§].

Concomitant Drug Class and/or Clearance Pathway: Drug Name	Effect on Concentration†	Clinical Comment
Immunosuppressants		
cyclosporine‡	↑ cyclosporine ↑ letermovir	Co-administration of PREVYMIS™ with cyclosporine increases concentrations of both letermovir and cyclosporine. When PREVYMIS™ is co-administered with cyclosporine (a potent OATP1B1/3 inhibitor), the dosage of PREVYMIS™ should be decreased to 240 mg once daily (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage adjustment and ACTION and CLINICAL PHARMACOLOGY, Pharmacokinetics). Frequent monitoring of cyclosporine whole blood concentrations should be performed during and at discontinuation of PREVYMIS™ and the dose of cyclosporine 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 §. When PREVYMIS™ is co-administered with cyclosporine, refer to the sirolimus product monograph for specific sirolimus dosing recommendations§.
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	↓omeprazole	Clinical monitoring and dose adjustment may be needed.
pantoprazole	↓ pantoprazole	Clinical monitoring and dose adjustment may be needed.
CYP2C9/19 Substrates		
Examples: phenytoin#, warfarin#	↓ concentrations of CYP2C9/19 substrates	PREVYMIS™ may decrease the plasma concentrations of CYP2C9/19 substrates. Frequent monitoring of phenytoin concentrations should be performed when phenytoin is co-administered with PREVYMIS™§. Frequent monitoring of INR should be performed while warfarin is co-administered with PREVYMIS™§.
CYP3A SubstratesÞ		
Examples: alfentanil, fentanyl, midazolam, quinidine[1]	↑ concentrations of CYP3A substrate	PREVYMIS™ may increase the plasma concentrations of CYP3A substrates. Frequent monitoring for adverse reactions related to CYP3A substrates is recommended during co-administration. Dose adjustment of CYP3A substrates may be needed§ (see WARNINGS AND PRECAUTIONS).

Concomitant Drug Class and/or Clearance Pathway: Drug Name	Effect on Concentration[†]	Clinical Comment
		When PREVYMIS™ is co-administered with a CYP3A substrate, refer to the CYP3A substrate product monograph for dosing of the CYP3A substrate with a moderate CYP3A inhibitor[§]. When PREVYMIS™ is co-administered with alfentanil, fentanyl, and midazolam, closely monitor patients for adverse reactions such as respiratory depression and prolonged sedation. When PREVYMIS™ is co-administered with quinidine, closely monitor patients for adverse reactions such as ventricular arrhythmia and hypotension. When PREVYMIS™ is co-administered with cyclosporine, the combined effect on CYP3A substrates may be similar to a strong CYP3A inhibitor. Refer to the CYP3A substrate product monograph for dosing of the CYP3A substrate with a strong CYP3A inhibitor[§].

[β] This table is not all inclusive.
[†] ↓ =decrease, ↑=increase
[‡] These interactions have been studied (see ACTION and CLINICAL PHARMACOLOGY, Pharmacokinetics).
[§] Refer to the respective product monograph.
[¶] Based on physiologically based pharmacokinetic modelling.
[#] Co-administration of PREVYMIS™ with phenytoin or warfarin has not been studied.
[Þ] Based on *in vivo* studies with midazolam. Refer to the respective product monograph.

Drugs without Clinically Significant Interactions with PREVMIS™
No clinically relevant drug-drug interaction is expected when PREVYMIS™ is co-administered with P-glycoprotein (P-gp) inhibitors.

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 (see below).

The interaction between letermovir and the following drugs was evaluated in clinical studies: mycophenolate mofetil, posaconazole, and oral combinations of ethinyl estradiol/levonorgestrel. No dose adjustments are needed when PREVYMIS™ is used with these drugs.

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 4 and Table 5).

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 cyclosporine (a potent OATP1B1/3 inhibitor), the recommended dose of PREVYMIS™ is 240 mg once daily (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment). Changes in letermovir plasma concentrations due to inhibition of P-gp are not anticipated to be clinically relevant. Inhibition of UGTs is not anticipated to have a clinically relevant effect on letermovir plasma concentrations. 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.

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 5). Based on these results, co-administration of PREVYMIS™ with CYP3A substrates may increase the plasma concentrations of the CYP3A substrates (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS, Drug-Drug Interactions, and Table 3). 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 3 in DRUG INTERACTIONS, Drug-Drug Interactions). 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 3 in DRUG INTERACTIONS, Drug-Drug Interactions). 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 3 in DRUG INTERACTIONS, Drug-Drug Interactions). 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 5). The effect of letermovir on BCRP, BSEP, and MRP2 substrates was not evaluated in clinical studies; the clinical relevance is unknown.

Table 4 - 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
Immunosuppressants					
cyclosporine	200 mg single dose PO	240 mg once daily PO	13	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 (0.93, 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					

Table 5 - 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, 2.49)	1.72 (1.54, 1.92)
P-gp Substrates					
digoxin	0.5 mg single dose PO	240 mg twice daily PO	22	0.88 (0.80, 0.96)	0.75 (0.63, 0.89)
Immunosuppressants					
cyclosporine	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)
Antifungals and Antiviral					
acyclovir	400 mg single dose PO	480 mg once daily PO	13	1.02 (0.87, 1.2)	0.82 (0.71, 0.93)
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					

8.4 Drug-Food Interactions

Food increases peak levels (C_{max}) but not exposure (AUC_T) of PREVYMIS™ following administration with a high fat, high calorie meal (see DOSAGE AND ADMINISTATION, Dosing Considerations and ACTION and CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption, Effect of Food).

8.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

8.6 Drug-Laboratory Test Interactions

Interactions with clinical laboratory tests have not been established.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

PREVYMIS™ is an antiviral drug against CMV (see MICROBIOLOGY).

9.2 Pharmacodynamics

Cardiac Electrophysiology
The effect of letermovir on doses up to 960 mg given IV on the QTc interval was evaluated in a randomized, single-dose, placebo- and active-controlled (moxifloxacin 400 mg oral) 4-period crossover thorough QT trial in 33 healthy subjects. Letermovir did 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.

9.3 Pharmacokinetics

The pharmacokinetics of letermovir have been characterized 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 45 minutes to 2.25 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 6). Differences in exposure across treatment regimens are not clinically relevant; efficacy was consistent across the range of exposures observed in P001.

Table 6 - Letermovir AUC (ng•hr/mL) Values in HSCT Recipients

Treatment Regimen	Median (90% Prediction Interval)[β]
480 mg Oral, no cyclosporine	34,400 (16,900, 73,700)
480 mg IV, no cyclosporine	100,000 (65,300, 148,000)
240 mg Oral, with cyclosporine	60,800 (28,700, 122,000)
240 mg IV, with cyclosporine	70,300 (46,200, 106,000)
[β] 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 cyclosporine. The inter-individual variability for bioavailability was estimated to be approximately 37%.

Effect of Cyclosporine
In HSCT recipients, co-administration of cyclosporine increased plasma concentrations of letermovir. Bioavailability of letermovir was estimated to be approximately 85% with 240 mg once daily oral PREVYMIS™ co-administered with cyclosporine. If PREVYMIS™ is co-administered with cyclosporine, the recommended dose of PREVYMIS™ is 240 mg once daily (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

Effect of Food
Relative to administration under fasting conditions, oral administration of a single 480 mg dose of PREVYMIS™ 480 mg tablets with a standard high fat, high calorie meal resulted in no significant effect on overall exposure (AUC_T) of letermovir and an increase in peak levels (C_{max}) of approximately 30%. The increase in C_{max} is not clinically relevant (see DOSAGE AND ADMINISTRATION, Dosing Considerations and DRUG INTERACTIONS, Drug-Food Interactions).

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.

In pregnant rats, letermovir was able to cross the placenta (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).

Metabolism: The majority of drug-related component in plasma is unchanged parent (96.6%).

No major metabolites are detected in plasma. Letermovir is partly eliminated by glucuronidation mediated by UGT1A1/1A3.

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).

Special Populations and Conditions

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

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

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

Genetic Polymorphism: 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.

Ethnic origin: 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.

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.

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/1.73m^2) and severe (eGFR less than 30 mL/min/1.73m^2) renal impairment, respectively, compared to healthy subjects. The changes in letermovir exposure due to renal impairment are not clinically relevant.

Combined Renal and Hepatic Impairment: Clinically relevant increases in letermovir exposure are anticipated in patients with moderate hepatic impairment combined with moderate or severe renal impairment.

Obesity: 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.

10 STORAGE, STABILITY AND DISPOSAL

Tablets and solution for injection:

Store PREVYMIS™ tablets in the original package until use.

Store PREVYMIS™ tablets at room temperature (15°C to 30°C).

Store PREVYMIS™ for injection vials at 20°C to 25°C. Store in the original carton to protect from exposure to light.

[1] Not marketed in Canada.

PART II: SCIENTIFIC INFORMATION

11 PHARMACEUTICAL INFORMATION

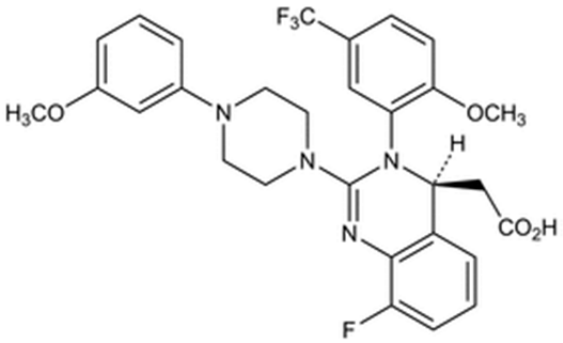
Drug Substance

Common name: letermovir

Chemical name: (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

Molecular formula and molecular mass: $C_{29}H_{28}F_4N_4O_4$, 572.55

Structural formula:



Physicochemical properties: Letermovir drug substance (DS) is amorphous powder, with two pKa values at 3.6 and 7.1. Letermovir exists predominantly in the zwitterion form between pH 4 and pH 7 with a low intrinsic solubility of approximately 0.3 mg/mL. Solubility increases above pH 7 to 7.7 mg/mL and 25.5 mg/mL at pH 8 and pH 9, respectively.

12 CLINICAL TRIALS

12.1 Trial Design and Study Demographics

Adult CMV-seropositive Recipients [R+] of an Allogeneic Hematopoietic Stem Cell Transplant (HSCT): A phase III study to evaluate the safety and efficacy of PREVYMIS™ in the prevention of clinically significant CMV infection in adult CMV-seropositive recipients [R+] of an allogeneic HSCT. A summary of trial design and demographics is presented in Table 7:

Table 7 - Summary of trial design and patient demographics for the phase III trial in HSCT recipients (P001)

Trial design	Dosage, route of administration and duration	Study subjects (n)	Age	Other Demographic Characteristics	Baseline Patient Characteristics
Randomized, double-blind, placebo-controlled, multi-site	PREVYMIS™: 480 mg QD or 240 mg QD dose, if given concomitantly with CsA, through Week 14 (~100 days) post-transplant; dose is the same for both oral tablets and IV formulation. Placebo: matching placebo oral tablets for letermovir oral tablets; normal saline or 5% dextrose as placebo comparator for IV letermovir formulation	Total: 565 PREVYMIS™: 373 Placebo: 192	Mean: 50.8 years Median: 54 years Range: (18 - 78 years)	Male: 58% Female: 42% 10% were Asian; 2% were Black or African; and 7% were Hispanic or Latino	The most common primary reasons for HCST were acute myeloid leukemia (38%), myeloblastic syndrome (15%), and lymphoma (13%). 50% of subjects received a myeloablative regimen, 52% were receiving cyclosporine, and 42% were receiving tacrolimus. Twelve percent (12%) of subjects were positive for CMV DNA at baseline.

Subjects were randomized (2:1) to receive either PREVYMIS™ or placebo. Randomization was stratified by investigational site and risk (high vs. low) 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. Subjects were monitored through Week 24 post-transplant for the primary efficacy endpoint.

At baseline, 31% of subjects were at high risk for reactivation 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.

12.2 Study Results

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 viremia (using the Roche COBAS* AmpliPrep/COBAS TaqMan* assay, Lower Limit of Quantification (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 8. The estimated treatment difference of -23.5% was statistically significant (one-sided p-value <0.0001).

Table 8 - P001 Efficacy Results in HSCT Recipients (NC=F Approach, FAS Population)

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

[β] 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 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 (high or low risk). A 1-sided p-value ≤0.0249 was used for declaring statistical significance.
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-transplant visit window.
N = number of subjects in each treatment group.
n (%) = Number (percent) of subjects in each sub-category.

At Week 14 post-transplant, the Kaplan-Meier (K-M) event rate for clinically significant CMV infection was 6.8% in the PREVYMIS™ group compared to 41.3% in the placebo group. At

Week 24 post-transplant, the 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). 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 randomization.

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.

Efficacy consistently favored PREVYMIS™ across subgroups including low and high risk for CMV reactivation, stem cell source, donor mismatch, haploidentical transplant, conditioning regimens, and concomitant immunosuppressive regimens.

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, and 23.8% vs. 27.6% at Week 48 post-transplant.

The K-M event rate for CMV-related mortality (defined as death due to any reason in patients with clinically significant CMV infection [primary endpoint]) in the letermovir vs. placebo group was 0.7% vs. 9.1% at Week 24 post-transplant (nominal two-sided stratified log-rank p-value < 0.0001), and 3.6% vs. 16.0% at Week 48 post-transplant (nominal two-sided stratified log rank p-value < 0.0001).

13 MICROBIOLOGY

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

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). There was no significant difference in EC_{50} value by CMV gB genotype (n=70).

Viral Resistance
In Cell Culture
The CMV genes UL56 and UL89 encode subunits of CMV DNA terminase. CMV mutants with reduced susceptibility to letermovir have been selected in cell culture. The mutations map to UL56 and occur in amino acid residues between 231 and 369 (V231A, V231L, V236L, V236M, E237D, L241P, T244K, T244R, L257I, F261C, F261L, F261S, Y321C, C325F, C325R, C325Y, M329T, R369G, R369M, R369S). EC_{50} values for these mutations are 2.1 to >3000-fold higher than those for the wild-type reference virus. EC_{50} ratios of >3000 are interpreted as absolute letermovir resistance, because viral yield reduction occurs at visibly cytotoxic letermovir concentrations. No known letermovir resistance mutations map to UL89.

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 22 letermovir-treated subjects, in the FAS population who experienced prophylaxis failure and for whom samples were available for analysis. One subject had a letermovir-resistant GV (V236M).

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). These DNA polymerase inhibitors are fully active against viral populations with substitutions conferring resistance to letermovir.

14 NON-CLINICAL TOXICOLOGY

General Toxicity
Testicular toxicity was noted only in rats at systemic exposures (AUC) ≥3-fold the exposures in humans at the recommended human dose (RHD). This toxicity was characterized by seminiferous tubular degeneration, and oligospermia and cell debris in the epididymides, with decreased testicular and epididymides weights. The No-Observed Adverse Effect Level (NOAEL) for testicular toxicity in rats was observed at exposures (AUC) in rats similar to the exposures in humans at the RHD. This testicular toxicity appears to be species-specific; testicular toxicity was not observed in mice and monkeys at the highest doses tested at exposures up to 4-fold and 2-fold, respectively, the exposures in humans at the RHD. The relevance to humans is unknown. (see ADVERSE REACTIONS, Abnormal Laboratory Findings).

Carcinogenicity
Carcinogenicity studies with letermovir have not been conducted.

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.

Reproductive and Developmental Toxicology
Reproduction
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 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 (see NON-CLINICAL TOXICOLOGY, General Toxicity).

Development
In pregnant rats, maternal toxicity (including decrease in body weight gain) was noted at the highest dose of 250 mg/kg/day (approximately 11-fold the AUC at the RHD); in the offspring, decreased fetal weight with delayed ossification, slightly edematous 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 up to the dose of 50 mg/kg/day (approximately 2.5-fold the AUC at the RHD).

In pregnant rabbits, maternal toxicity (including mortality and abortions) was noted at the highest dose of 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 up to the dose of 75 mg/kg/day (at less than the AUC at the RHD).

In the pre- and post-natal developmental study, no developmental toxicity was observed up to the highest exposure of 180 mg/kg/day (2-fold the AUC at the RHD).

Lactation

No effects of letermovir on growth and postnatal development were observed in nursing rat pups at the highest dose tested (at 2-fold the AUC at the RHD) (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

℞ PREVYMIS™
letermovir tablets
letermovir for injection

Read this carefully before you start taking **PREVYMIS™ (letermovir)** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **PREVYMIS™**.

What is PREVYMIS™ used for?
PREVYMIS™ is a medicine to help to keep adults 18 years of age and older from getting ill from CMV (cytomegalovirus*).* CMV is a virus that a lot of people have, but they don't even know it. For most people, CMV just stays in their body and it doesn't hurt them. However, if your immune system is weak after you get a bone marrow transplant, you may be at high risk of becoming ill from CMV.

How does PREVYMIS™ work?
PREVYMIS™ is an antiviral medicine. It stops CMV from multiplying.

What are the ingredients in PREVYMIS™?
Medicinal ingredients: letermovir

PREVYMIS™ is available as either a tablet or an IV

Non-medicinal ingredients:

- Tablets: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and povidone 25.

  The tablets are film-coated with a coating material containing the following inactive ingredients: hypromellose 2910, iron oxide yellow, and (only for 480 mg tablets) iron oxide red, lactose monohydrate, titanium dioxide and triacetin. Carnauba wax is added as a polishing agent.

- Injection (IV): hydroxypropyl betadex, sodium chloride, sodium hydroxide, and Water for Injection.

PREVYMIS™ comes in the following dosage forms:
Tablet: 240 mg and 480 mg
Solution for injection: 20 mg/mL. Available in 240 mg/12mL and 480 mg/24 mL

Do not use PREVYMIS™ if you:

- are allergic to letermovir, or any of the other ingredients of PREVYMIS™.
- are taking any of the following medicines:
  - Pimozide (for Tourette's syndrome).
  - Ergot alkaloids (for migraine headaches).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PREVYMIS™. Talk about any health conditions or problems you may have, including if you:

- have kidney disease.
- have liver disease.
- are a pregnant women or trying to get pregnant. It is not known if PREVYMIS™ will harm your baby while you are pregnant.
- are breast-feeding or plan to breast-feed. It is not known if PREVYMIS™ gets in your breast milk and will be passed to your baby.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with PREVYMIS™:

- If you take any of these medicines, be sure to tell your doctor:
    - Alfentanil, fentanyl (for severe pain)
    - Midazolam (used as a sedative)
    - Cyclosporine, tacrolimus, sirolimus (used to prevent transplant rejection)
    - Voriconazole (for fungal infections)
    - Statins, such as atorvastatin, simvastatin, fluvastatin, pravastatin, rosuvastatin (for high cholesterol)
    - Glyburide, repaglinide, rosiglitazone (for high blood sugar)
    - Phenytoin (for seizures or convulsions)
    - Warfarin (used as a blood thinner or for blood clots)
    - Amiodarone (used to correct irregular heartbeats)
    - Omeprazole, pantoprazole (for stomach ulcers and other stomach problems)
- Know the medicines you take. Keep a list of medicines and show it to your doctor and pharmacist when you get a new medicine.
- You can ask your doctor or pharmacist for a list of medicines that may interact with PREVYMIS™.
- Do not start or stop taking another medicine without telling your doctor first.

How to take PREVYMIS™:
You can receive PREVYMIS™ two different ways: as tablets or through an IV (intravenously). It is important that you do not miss or skip doses of PREVYMIS™.

Usual adult dose:

If you take the tablets:

- **Take 1 tablet once a day.**
    - Take it at the same time every day.
    - Take it with or without food.
    - Swallow the tablet whole. Do not break, crush, or chew the tablet.
- Take this medicine exactly how your doctor tells you to take it.
- Keep it in the original package until you are ready to take it.
- Do not stop taking PREVYMIS™ without talking to your doctor first.

- Do not run out of your PREVYMIS™.

If you receive PREVYMIS™ through an IV (intravenously):
- You will receive PREVYMIS™ once a day and it will take about 1 hour.

Overdose:
If you take more PREVYMIS™, than your prescribed dose, call your doctor right away.

If you think you have taken too much PREVYMIS™, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take the tablets:
If you forget to take your dose of PREVYMIS™, take it as soon as you remember.
If you do not remember until it is almost time for your next dose, skip your last dose and take the next dose at your usual time.
- Do not take two doses of PREVYMIS™ at the same time to make up for a missed dose.
- If you are not sure what to do, call your doctor or pharmacist.

If you receive PREVYMIS™ through an IV (intravenously):
- If you miss your appointment, reschedule it right away.

What are possible side effects from using PREVYMIS™?

These are not all the possible side effects you may feel when taking PREVYMIS™. If you experience any side effects not listed here, contact your healthcare professional.

Common side effects of PREVYMIS™:
- nausea
- diarrhea
- vomiting

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Tablet and solution for injection:

- Keep PREVYMIS™ in the original package until you are ready to take it.
- Keep PREVYMIS™ tablets at room temperature (15°C to 30°C).
- If you have to keep PREVYMIS™ injection at home, keep it at room temperature (20°C to 25°C). Protect from light.

Keep out of reach and sight of children.

If you want more information about PREVYMIS™:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php) or the Merck Canada webiste www.merck.ca or by calling 1-800-567-2594.

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