▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

PREVYMIS 240 mg concentrate for solution for infusion
PREVYMIS 480 mg concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PREVYMIS 240 mg concentrate for solution for infusion
Each vial contains 240 mg (12 mL per vial) of letermovir.
Each mL contains 20 mg of letermovir.

PREVYMIS 480 mg concentrate for solution for infusion
Each vial contains 480 mg (24 mL per vial) of letermovir.
Each mL contains 20 mg of letermovir.

Excipient with known effect
This medicinal product contains 23 mg (1.0 mmol) sodium per 240 mg vial, equivalent to 1.15% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
This medicinal product contains 46 mg (2.0 mmol) sodium per 480 mg vial, equivalent to 2.30% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Each 240 mg dose (12 mL vial) of this medicinal product contains 1800 mg hydroxypropylbetadex (cyclodextrin).
Each 480 mg dose (24 mL vial) of this medicinal product contains 3600 mg hydroxypropylbetadex (cyclodextrin).
For additional information, see section 4.2.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)
Clear, colourless liquid
pH between 7 and 8

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

PREVYMIS is indicated for prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT).

Consideration should be given to official guidance on the appropriate use of antiviral agents.

### 4.2 Posology and method of administration

PREVYMIS should be initiated by a physician experienced in the management of patients who have had an allogeneic haematopoietic stem cell transplant.

Posology
PREVYMIS is also available for oral administration (240 mg and 480 mg film-coated tablets).

PREVYMIS tablets and concentrate for solution for infusion may be used interchangeably at the discretion of the physician, and no dose adjustment is necessary.

The recommended dosage of PREVYMIS is 480 mg once daily.

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

The safety and efficacy of letermovir use for more than 100 days has not been studied in clinical trials. Prolonged letermovir prophylaxis beyond 100 days post-transplant may be of benefit in some patients at high risk for late CMV reactivation (see section 5.1). Use of letermovir prophylaxis for greater than 100 days requires a careful assessment of the benefit-risk balance.

*Dosage adjustment*
If PREVYMIS is co-administered with cyclosporine, the dosage of PREVYMIS should be decreased to 240 mg once daily (see sections 4.5 and 5.2).
- 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.

*Missed dose*
If a dose is missed, it should be given to the patient as soon as possible. If it is time for the next dose, skip the missed dose and go back to the regular schedule. Do not double the next dose or give more than the prescribed dose.

Special populations

*Elderly*
No dose adjustment of PREVYMIS is required based on age (see sections 5.1 and 5.2).

*Hepatic impairment*
No dose adjustment of PREVYMIS is required based on mild (Child-Pugh Class A) to moderate (Child-Pugh Class B) hepatic impairment. PREVYMIS is not recommended for patients with severe (Child-Pugh Class C) hepatic impairment (see section 5.2).

*Combined hepatic and renal impairment*
PREVYMIS is not recommended in patients with moderate hepatic impairment combined with moderate or severe renal impairment (see section 5.2).

*Renal impairment*
No dose adjustment of PREVYMIS is recommended for patients with mild, moderate, or severe renal impairment. No dose recommendation can be made for patients with end stage renal disease (ESRD) with or without dialysis. Efficacy and safety has not been demonstrated for patients with ESRD.

PREVYMIS concentrate for solution for infusion contains hydroxypropylbetadex. The anticipated clinical exposure to hydroxypropylbetadex with intravenously administered letermovir is expected to be approximately 3600 mg/day for a letermovir dose of 480 mg. There were no cases of kidney injury caused by hydroxypropylbetadex in human studies of intravenously administered letermovir with treatment durations of up to 47 days. In patients with moderate or severe renal impairment (creatinine

clearance less than 50 mL/min) receiving PREVYMIS, accumulation of hydroxypropylbetadex, could occur (see section 5.3). Serum creatinine levels should be closely monitored in these patients.

*Paediatric population*
The safety and efficacy of PREVYMIS in patients below 18 years of age have not been established. No data are available (see section 5.1).

Method of administration
For intravenous use only.
PREVYMIS concentrate for solution for infusion requires dilution (see section 6.6) prior to administration.
PREVYMIS diluted solution must be administered through a sterile 0.2 micron or 0.22 micron polyethersulfone (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.
PREVYMIS should be administered as an intravenous (IV) infusion only. PREVYMIS should not be administered as an intravenous push or bolus.
After dilution, PREVYMIS should be administered by intravenous infusion via peripheral or central venous catheter using a total time of approximately 60 minutes. The entire contents of the IV bag should be administered.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Concomitant administration with pimozide (see sections 4.4 and 4.5).
Concomitant administration with ergot alkaloids (see sections 4.4 and 4.5).
Concomitant administration with St. John's wort *(Hypericum perforatum)* (see section 4.5).
When letermovir is combined with cyclosporine:
Concomitant use of dabigatran, atorvastatin, simvastatin, rosuvastatin or pitavastatin is contraindicated (see section 4.5).

## 4.4 Special warnings and precautions for use

Monitoring of CMV DNA
The safety and efficacy of letermovir has been established in patients with a negative CMV DNA test result prior to initiation of prophylaxis. CMV DNA was monitored on a weekly basis until post-transplant Week 14, and subsequently bi-weekly until Week 24. In cases of clinically significant CMV DNAemia or disease, letermovir prophylaxis was stopped and standard-of-care pre-emptive therapy (PET) or treatment was initiated. In patients in whom letermovir prophylaxis was initiated and the baseline CMV DNA test was subsequently found to be positive, prophylaxis could be continued if PET criteria had not been met (see section 5.1).

Risk of adverse reactions or reduced therapeutic effect due to medicinal product interactions
The concomitant use of PREVYMIS and certain medicinal products may result in known or potentially significant medicinal product interactions, some of which may lead to:

- possible clinically significant adverse reactions from greater exposure of concomitant medicinal products or letermovir.
- significant decrease of concomitant medicinal product plasma concentrations which may lead to reduced therapeutic effect of the concomitant medicinal product.

See Table 1 for steps to prevent or manage these known or potentially significant medicinal product interactions, including dosing recommendations (see sections 4.3 and 4.5).

Drug interactions
PREVYMIS should be used with caution with medicinal products that are CYP3A substrates with narrow therapeutic ranges (e.g., alfentanil, fentanyl, and quinidine) as co-administration may result in increases in the plasma concentrations of CYP3A substrates. Close monitoring and/or dose adjustment of co-administered CYP3A substrates is recommended (see section 4.5).

Increased monitoring of cyclosporine, tacrolimus, sirolimus is generally recommended the first 2 weeks after initiating and ending letermovir (see section 4.5) as well as after changing route of administration of letermovir.

Letermovir is a moderate inducer of enzymes and transporters. Induction may give rise to reduced plasma concentrations of some metabolised and transported medicinal products (see section 4.5). Therapeutic drug monitoring (TDM) is therefore recommended for voriconazole.
Concomitant use of dabigatran should be avoided due to risk of reduced dabigatran efficacy.

Letermovir may increase the plasma concentrations of medicinal products transported by OATP1B1/3 such as many of the statins (see section 4.5 and Table 1).

Administration through a sterile 0.2 or 0.22 micron PES in-line filter
PREVYMIS concentrate for solution for infusion may contain a few product-related small translucent or white particles. Administration of PREVYMIS diluted solution always requires the use of a sterile 0.2 micron or 0.22 micron PES in-line filter, regardless of whether these product-related particles are visible in the vial or diluted solution (see sections 4.2 and 6.6).

Excipients
PREVYMIS 240 mg concentrate for solution for infusion contains 23 mg (or 1.0 mmol) sodium per dose. This should be taken into consideration by patients on a controlled sodium diet.
PREVYMIS 480 mg concentrate for solution for infusion contains 46 mg (or 2.0 mmol) sodium per dose. This should be taken into consideration by patients on a controlled sodium diet.

## 4.5 Interaction with other medicinal products and other forms of interaction

General information about differences in exposure between different letermovir treatment regimens
-The estimated letermovir plasma exposure is different depending on the dose regimen used (see table in section 5.2). Therefore, the clinical consequences of drug interactions for letermovir will be dependent on which letermovir regimen is used and whether or not letermovir is combined with cyclosporine.
-The combination of cyclosporine and letermovir may lead to more marked or additional effects on concomitant medicinal products as compared to letermovir alone (see Table 1).

Effect of other medicinal products on letermovir
The elimination pathways of letermovir *in vivo* are biliary excretion and glucuronidation. The relative importance of these pathways is unknown. Both elimination pathways involve active uptake into the hepatocyte through the hepatic uptake transporters OATP1B1/ 3. After uptake, glucuronidation of letermovir is mediated by UGT1A1 and 3. Letermovir also appears to be subject to P-gp and BCRP mediated efflux in the liver and intestine (see section 5.2).

Inducers of drug metabolizing enzymes or transporters
Co-administration of PREVYMIS (with or without cyclosporine) with strong and moderate inducers of transporters (e.g., P-gp) and/or enzymes (e.g., UGTs) is not recommended, as it may lead to subtherapeutic letermovir exposure (see Table 1).
-Examples of strong inducers include rifampicin, phenytoin, carbamazepine, St. John's wort (*Hypericum perforatum*), rifabutin and phenobarbital.
-Examples of moderate inducers include thioridazine, modafinil, ritonavir, lopinavir, efavirenz and etravirine.

Rifampicin co-administration resulted in an initial increase in letermovir plasma concentrations (due to OATP1B1/3 and/or P-gp inhibition) that is not clinically relevant, followed by clinically relevant decreases in letermovir plasma concentrations (due to induction of P-gp/UGT) with continued rifampicin co-administration (see Table 1).

Additional effects of other products on letermovir relevant when combined with cyclosporine

*Inhibitors of OATP1B1 or 3*
Co-administration of PREVYMIS with medicinal products that are inhibitors of OATP1B1/3 transporters may result in increased 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 Table 1 and sections 4.2 and 5.2). Caution is advised if other OATP1B1/3 inhibitors are added to letermovir combined with cyclosporine.
-Examples of OATP1B1 inhibitors include gemfibrozil, erythromycin, clarithromycin, and several protease inhibitors (atazanavir, simeprevir).

*Inhibitors of P-gp/BCRP*
*In vitro* results indicate that letermovir is a substrate of P-gp/BCRP. Changes in letermovir plasma concentrations due to inhibition of P-gp/BCRP by itraconazole were not clinically relevant.

Effect of letermovir on other medicinal products

*Medicinal products mainly eliminated through metabolism or influenced by active transport*
Letermovir is a general inducer *in vivo* of enzymes and transporters. Unless a particular enzyme or transporter is also inhibited (see below) induction can be expected. Therefore, letermovir may potentially lead to decreased plasma exposure and possibly reduced efficacy of co-administered medicinal products that are mainly eliminated through metabolism or by active transport.
The size of the induction effect is dependent on letermovir route of administration and whether cyclosporine is concomitantly used.
The full induction effect can be expected after 10-14 days of letermovir treatment. The time needed to reach steady state of a specific affected medicinal product will also influence the time needed to reach full effect on the plasma concentrations.

*In vitro*, letermovir is an inhibitor of CYP3A, CYP2C8, CYP2B6, BCRP, UGT1A1, OATP2B1, and OAT3 at *in vivo* relevant concentrations. *In vivo* studies are available investigating the net effect on CYP3A4, P-gp, OATP1B1/3 additionally on CYP2C19. The net effect *in vivo* on the other listed enzymes and transporters is not known. Detailed information is presented below.
It is unknown whether letermovir may affect the exposure of piperacillin/tazobactam, amphotericine B and micafungin. The potential interaction between letermovir and these medicinal products have not been investigated. There is a theoretical risk of reduced exposure due to induction but the size of the effect and thus clinical relevance is presently unknown.

*Medicinal products metabolised by CYP3A*
Letermovir is a moderate inhibitor of CYP3A *in vivo*. Co-administration of PREVYMIS with oral midazolam (a CYP3A substrate) results in 2-3-fold increased midazolam plasma concentrations. Co-administration of PREVYMIS may result in clinically relevant increases in the plasma concentrations of co-administered CYP3A substrates (see sections 4.3, 4.4, and 5.2).
-Examples of such medicinal products include certain immunosuppressants (e.g., cyclosporine, tacrolimus, sirolimus), HMG-CoA reductase inhibitors, and amiodarone (see Table 1). Pimozide and ergot alkaloids are contraindicated (see section 4.3).
The size of the CYP3A inhibitory effect is dependent on letermovir route of administration and whether cyclosporine is concomitantly used.
Due to time dependent inhibition and simultaneous induction the net enzyme inhibitory effect may not be reached until after 10-14 days. The time needed to reach steady state of a specific affected medicinal product will also influence the time needed to reach full effect on the plasma concentrations. When ending treatment, it takes 10-14 days for the inhibitory effect to disappear. If monitoring is applied, this is recommended the first 2 weeks after initiating and ending letermovir (see section 4.4) as well as after changing route of letermovir administration.

*Medicinal products transported by OATP1B1/3*
Letermovir is an inhibitor of OATP1B1/3 transporters. Administration of PREVYMIS may result in a clinically relevant increase in plasma concentrations of co-administered medicinal products that are OATP1B1/3 substrates.
-Examples of such medicinal products include HMG-CoA reductase inhibitors, fexofenadine, repaglinide and glyburide (see Table 1). Comparing letermovir regimen administered without cyclosporine, the effect is more marked after iv than oral letermovir.
The magnitude of the OATP1B1/3 inhibition on co-administered medicinal products is likely greater when PREVYMIS is co-administered with cyclosporine (a potent OATP1B1/3 inhibitor). This needs to be considered when the letermovir regimen is changed during treatment with an OATP1B1/3 substrate.

*Medicinal products metabolised by CYP2C9 and/or CYP2C19*
Co-administration of PREVYMIS with voriconazole (a CYP2C19 substrate) results in significantly decreased voriconazole plasma concentrations, indicating that letermovir is an inducer of CYP2C19. CYP2C9 is likely also induced. Letermovir has the potential to decrease the exposure of CYP2C9 and/or CYP2C19 substrates potentially resulting in subtherapeutic levels.
-Examples of such medicinal products include warfarin, voriconazole, diazepam, lansoprazole, omeprazole, esomeprazole, pantoprazole, tilidine, tolbutamide (see Table 1).
The effect is expected to be less pronounced for oral letermovir without cyclosporine, than IV letermovir with or without cyclosporine, or oral letermovir with cyclosporine. This needs to be considered when the letermovir regimen is changed during treatment with a CYP2C9 or CYP2C19 substrate. See also general information on induction above regarding time courses of the interaction.

*Medicinal products metabolised by CYP2C8*
Letermovir inhibits CYP2C8 *in vitro* but may also induce CYP2C8 based on its induction potential. The net effect *in vivo* is unknown.
-An example of a medicinal product which is mainly eliminated by CYP2C8 is repaglinide (see Table 1). Concomitant use of repaglinide and letermovir with or without cyclosporine is not recommended.

*Medicinal products transported by P-gp in the intestine*
Letermovir is an inducer of intestinal P-gp. Administration of PREVYMIS may result in a clinically relevant decrease in plasma concentrations of co-administered medicinal products that are significantly transported by P-gp in the intestine such as dabigatran and sofosbuvir.

*Medicinal products metabolised by CYP2B6, UGT1A1 or transported by BCRP or OATP2B1*
Letermovir is a general inducer *in viv*o but has also been observed to inhibit CYP2B6, UGT1A1, BCRP, and OATP2B1 *in vitro*. The net effect *in vivo* is unknown. Therefore, the plasma concentrations of medicinal products that are substrates of these enzymes or transporters may increase or decrease when co-administered with letermovir. Additional monitoring may be recommended; refer to the prescribing information for such medicinal products.
-Examples of medicinal products that are metabolised by CYP2B6 include bupropion.
-Examples of medicinal products metabolised by UGT1A1 are raltegravir and dolutegravir.
-Examples of medicinal products transported by BCRP include rosuvastatin and sulfasalazine.
-An example of medicinal product transported by OATP2B1 is celiprolol.

*Medicinal products transported by the renal transporter OAT3*
*In vitro* data indicate that letermovir is an inhibitor of OAT3; therefore, letermovir may be an OAT3 inhibitor *in vivo*. Plasma concentrations of medicinal products transported by OAT3 may be increased.
-Examples of medicinal products transported by OAT3 includes ciprofloxacin, tenofovir, imipenem, and cilastin.

<u>General information</u>
If dose adjustments of concomitant medicinal products are made due to treatment with PREVYMIS, doses should be readjusted after treatment with PREVYMIS is completed. A dose adjustment may also be needed when changing route of administration or immunosuppressant.

Table 1 provides a listing of established or potentially clinically significant medicinal product interactions. The medicinal product interactions described are based on studies conducted with PREVYMIS or are predicted medicinal product interactions that may occur with PREVYMIS (see sections 4.3, 4.4, 5.1, and 5.2).

**Table 1: Interactions and dose recommendations with other medicinal products. Note that the table is not extensive but provides examples of clinically relevant interactions. See also the general text on DDIs above.**

**Unless otherwise specified, interaction studies have been performed with oral letermovir without cyclosporine. Please note that the interaction potential and clinical consequences may be different depending on whether letermovir is administered orally or IV, and whether cyclosporine is concomitantly used. When changing the route of administration, or if changing immunosuppressant, the recommendation concerning co-administration should be revisited.**

| **Concomitant medicinal product** | **Effect on concentration[†] Mean ratio (90 % confidence interval) for AUC, $C_{max}$ (likely mechanism of action)** | **Recommendations concerning co-administration with PREVYMIS** |
|---|---|---|
| **Antibiotics** | | |
| nafcillin | Interaction not studied.<br>Expected:<br>↓ letermovir<br><br>(P-gp/UGT induction) | Nafcillin may decrease plasma concentrations of letermovir.<br>Co-administration of PREVYMIS and nafcillin is not recommended. |
| **Antifungals** | | |
| fluconazole (400 mg single dose)/letermovir (480 mg single dose) | ↔ fluconazole<br>AUC 1.03 (0.99, 1.08)<br>$C_{max}$ 0.95 (0.92, 0.99)<br>↔ letermovir<br>AUC 1.11 (1.01, 1.23)<br>$C_{max}$ 1.06 (0.93, 1.21)<br><br>Interaction at steady state not studied.<br>Expected;<br>↔ fluconazole<br>↔ letermovir | No dose adjustment required. |
| itraconazole (200 mg once daily PO)/letermovir (480 mg once daily PO) | ↔ itraconazole<br>AUC 0.76 (0.71, 0.81)<br>$C_{max}$ 0.84 (0.76, 0.92)<br><br>↔ letermovir<br>AUC 1.33 (1.17, 1.51)<br>$C_{max}$ 1.21 (1.05, 1.39) | No dose adjustment required. |
| posaconazole[‡] (300 mg single dose)/ letermovir (480 mg daily) | ↔ posaconazole<br>AUC 0.98 (0.82, 1.17)<br>$C_{max}$ 1.11 (0.95, 1.29) | No dose adjustment required. |
| voriconazole[‡] (200 mg twice daily)/ letermovir (480 mg daily) | ↓ voriconazole<br>AUC 0.56 (0.51, 0.62)<br>$C_{max}$ 0.61 (0.53, 0.71)<br><br>(CYP2C9/19 induction) | If concomitant administration is necessary, TDM for voriconazole is recommended the first 2 weeks after initiating or ending letermovir, as well as after changing route of administration of letermovir or immunosuppressant. |

| Concomitant medicinal product | Effect on concentration† Mean ratio (90 % confidence interval) for AUC, $C_{max}$ (likely mechanism of action) | Recommendations concerning co-administration with PREVYMIS |
|---|---|---|
| **Antimycobacterials** | | |
| rifabutin | Interaction not studied.<br>Expected:<br>↓ letermovir<br><br>(P-gp/UGT induction) | Rifabutin may decrease plasma concentrations of letermovir.<br>Co-administration of PREVYMIS and rifabutin is not recommended. |
| Rifampicin | | Multiple dose rifampicin decreases plasma concentrations of letermovir.<br>Co-administration of PREVYMIS and rifampicin is not recommended. |
| (600 mg single dose PO)/ letermovir (480 mg single dose PO) | ↔ letermovir<br>AUC 2.03 (1.84, 2.26)<br>$C_{max}$ 1.59 (1.46, 1.74)<br>$C_{24}$ 2.01 (1.59, 2.54)<br><br>(OATP1B1/3 and/or P-gp inhibition) | |
| (600 mg single dose IV)/ letermovir (480 mg single dose PO) | ↔ letermovir<br>AUC 1.58 (1.38, 1.81)<br>$C_{max}$ 1.37 (1.16, 1.61)<br>$C_{24}$ 0.78 (0.65, 0.93)<br><br>(OATP1B1/3 and/or P-gp inhibition) | |
| (600 mg once daily PO)/ letermovir (480 mg once daily PO) | ↓ letermovir<br>AUC 0.81 (0.67, 0.98)<br>$C_{max}$ 1.01 (0.79, 1.28)<br>$C_{24}$ 0.14 (0.11, 0.19)<br><br>(Sum of OATP1B1/3 and/or P-gp inhibition and P-gp/UGT induction) | |
| (600 mg once daily PO (24 hours after rifampicin))§/ letermovir (480 mg once daily PO) | ↓ letermovir<br>AUC 0.15 (0.13, 0.17)<br>$C_{max}$ 0.27 (0.22, 0.31)<br>$C_{24}$ 0.09(0.06, 0.12)<br><br>(P-gp/UGT induction) | |
| **Antipsychotics** | | |
| thioridazine | Interaction not studied.<br>Expected:<br>↓ letermovir<br><br>(P-gp/UGT induction) | Thioridazine may decrease plasma concentrations of letermovir.<br>Co-administration of PREVYMIS and thioridazine is not recommended. |
| **Endothelin antagonists** | | |
| bosentan | Interaction not studied.<br>Expected:<br>↓ letermovir<br><br>(P-gp/UGT induction) | Bosentan may decrease plasma concentrations of letermovir.<br>Co-administration of PREVYMIS and bosentan is not recommended. |
| **Antivirals** | | |
| acyclovir‡ (400 mg single dose)/ letermovir (480 mg daily) | ↔ acyclovir<br>AUC 1.02 (0.87, 1.2)<br>$C_{max}$ 0.82 (0.71, 0.93) | No dose adjustment required. |

| **Concomitant medicinal product** | **Effect on concentration[†] Mean ratio (90 % confidence interval) for AUC, $C_{max}$ (likely mechanism of action)** | **Recommendations concerning co-administration with PREVYMIS** |
|---|---|---|
| valacyclovir | Interaction not studied.<br>Expected:<br>↔ valacyclovir | No dose adjustment required. |
| **Herbal products** | | |
| St. John's wort (*Hypericum perforatum*) | Interaction not studied.<br>Expected:<br>↓ letermovir<br><br>(P-gp/UGT induction) | St. John's wort may decrease plasma concentrations of letermovir.<br>Co-administration of PREVYMIS and St. John's wort is contraindicated. |
| **HIV medicinal products** | | |
| efavirenz | Interaction not studied.<br>Expected:<br>↓ letermovir<br>(P-gp/UGT induction)<br><br>↑ or ↓ efavirenz<br>(CYP2B6 inhibition or induction) | Efavirenz may decrease plasma concentrations of letermovir.<br>Co-administration of PREVYMIS and efavirenz is not recommended. |
| etravirine, nevirapine, ritonavir, lopinavir | Interaction not studied.<br>Expected:<br>↓ letermovir<br><br>(P-gp/UGT induction) | These antivirals may decrease plasma concentrations of letermovir.<br>Co-administration of PREVYMIS with these antivirals is not recommended. |
| **HMG-CoA reductase inhibitors** | | |
| atorvastatin[‡] (20 mg single dose)/ letermovir (480 mg daily) | ↑ atorvastatin<br>AUC 3.29 (2.84, 3.82)<br>$C_{max}$ 2.17 (1.76, 2.67)<br><br>(CYP3A, OATP1B1/3 inhibition) | Statin-associated adverse events such as myopathy should be closely monitored. The dose of atorvastatin should not exceed 20 mg daily when co-administered with PREVYMIS[#].<br><br>Although not studied, when PREVYMIS is co-administered with cyclosporine, the magnitude of the increase in atorvastatin plasma concentrations is expected to be greater than with PREVYMIS alone.<br>When PREVYMIS is co-administered with cyclosporine, atorvastatin is contraindicated. |
| simvastatin, pitavastatin, rosuvastatin | Interaction not studied.<br>Expected:<br>↑ HMG-CoA reductase inhibitors<br><br>(CYP3A, OATP1B1/3 inhibition) | Letermovir may substantially increase plasma concentrations of these statins.<br>Concomitant use is not recommended with PREVYMIS alone.<br><br>When PREVYMIS is co-administered with cyclosporine, use of these statins is contraindicated. |

| **Concomitant medicinal product** | **Effect on concentration[†] Mean ratio (90 % confidence interval) for AUC, $C_{max}$ (likely mechanism of action)** | **Recommendations concerning co-administration with PREVYMIS** |
|---|---|---|
| fluvastatin, pravastatin | Interaction not studied.<br>Expected:<br>↑ HMG-CoA reductase inhibitors<br><br>(OATP1B1/3 and/or BCRP inhibition) | Letermovir may increase statin plasma concentrations.<br><br>When PREVYMIS is co-administered with these statins, a statin dose reduction may be necessary[#]. Statin-associated adverse events such as myopathy should be closely monitored.<br><br>When PREVYMIS is co-administered with cyclosporine, pravastatin is not recommended while for fluvastatin, a dose reduction may be necessary[#]. Statin-associated adverse events such as myopathy should be closely monitored. |
| **Immunosuppressants** | | |
| cyclosporine (50 mg single dose)/ letermovir (240 mg daily) | ↑ cyclosporine<br>AUC 1.66 (1.51, 1.82)<br>$C_{max}$ 1.08 (0.97, 1.19)<br>(CYP3A inhibition) | If PREVYMIS is co-administered with cyclosporine, the dosage of PREVYMIS should be decreased to 240 mg once daily (see sections 4.2 and 5.1).<br><br>Frequent monitoring of cyclosporine whole blood concentrations should be performed during treatment, when changing PREVYMIS administration route, and at discontinuation of PREVYMIS and the dose of cyclosporine adjusted accordingly[#]. |
| cyclosporine (200 mg single dose)/ letermovir (240 mg daily) | ↑ letermovir<br>AUC 2.11 (1.97, 2.26)<br>$C_{max}$ 1.48 (1.33, 1.65)<br><br>(OATP1B1/3 inhibition) | |
| mycophenolate mofetil (1 g single dose)/ letermovir (480 mg daily) | ↔mycophenolic acid<br>AUC 1.08 (0.97, 1.20)<br>$C_{max}$ 0.96 (0.82, 1.12)<br><br>↔ letermovir<br>AUC 1.18 (1.04, 1.32)<br>$C_{max}$ 1.11 (0.92, 1.34) | No dose adjustment required. |

| **Concomitant medicinal product** | **Effect on concentration[†] Mean ratio (90 % confidence interval) for AUC, $C_{max}$ (likely mechanism of action)** | **Recommendations concerning co-administration with PREVYMIS** |
|---|---|---|
| sirolimus[‡] (2 mg single dose)/ letermovir (480 mg daily) | ↑ sirolimus<br>AUC 3.40 (3.01, 3.85)<br>$C_{max}$ 2.76 (2.48, 3.06)<br><br>(CYP3A inhibition)<br><br>Interaction not studied.<br>Expected:<br>↔ letermovir | Frequent monitoring of sirolimus whole blood concentrations should be performed during treatment, when changing PREVYMIS administration route, and at discontinuation of PREVYMIS and the dose of sirolimus adjusted accordingly[#].<br>Frequent monitoring of sirolimus concentrations is recommended at initiation or discontinuation of cyclosporine co-administration with PREVYMIS.<br><br>When PREVYMIS is co-administered with cyclosporine, also refer to the sirolimus prescribing information for specific dosing recommendations for use of sirolimus with cyclosporine.<br><br>When PREVYMIS is co-administered with cyclosporine, the magnitude of the increase in concentrations of sirolimus may be greater than with PREVYMIS alone. |
| tacrolimus (5 mg single dose)/ letermovir (480 mg daily) | ↑ tacrolimus<br>AUC 2.42 (2.04, 2.88)<br>$C_{max}$ 1.57 (1.32, 1.86)<br>(CYP3A inhibition) | Frequent monitoring of tacrolimus whole blood concentrations should be performed during treatment, when changing PREVYMIS administration route, and at discontinuation of PREVYMIS and the dose of tacrolimus adjusted accordingly[#]. |
| tacrolimus (5 mg single dose)/ letermovir (80 mg twice daily) | ↔ letermovir<br>AUC 1.02 (0.97, 1.07)<br>$C_{max}$ 0.92 (0.84, 1.00) | |
| **Oral contraceptives** | | |
| ethinylestradiol (EE) (0.03 mg)/ levonorgestrel (LNG)[‡] (0.15 mg) single dose/ letermovir (480 mg daily) | ↔ EE<br>AUC 1.42 (1.32, 1.52)<br>$C_{max}$ 0.89 (0.83, 0.96)<br><br>↔ LNG<br>AUC 1.36 (1.30, 1.43)<br>$C_{max}$ 0.95 (0.86, 1.04) | No dose adjustment required. |
| Other systemically acting oral contraceptive steroids | Risk of ↓ contraceptive steroids | Letermovir may reduce plasma concentrations of other oral contraceptive steroids thereby affecting their efficacy.<br>For adequate contraceptive effect to be ensured with an oral contraceptive, products containing EE and LNG should be chosen. |

| Concomitant medicinal product | Effect on concentration† Mean ratio (90 % confidence interval) for AUC, $C_{max}$ (likely mechanism of action) | Recommendations concerning co-administration with PREVYMIS |
|---|---|---|
| **Antidiabetic medicinal products** | | |
| repaglinide | Interaction not studied.<br>Expected:<br>↑ or ↓ repaglinide<br><br>(CYP2C8 induction, CYP2C8 and OATP1B inhibition) | Letermovir may increase or decrease the plasma concentrations of repaglinide. (The net effect is not known).<br><br>Concomitant use is not recommended.<br><br>When PREVYMIS is co-administered with cyclosporine, the plasma concentrations of repaglinide is expected to increase due to the additional OATP1B inhibition by cyclosporine. Concomitant use is not recommended#. |
| glyburide | Interaction not studied.<br>Expected:<br>↑ glyburide<br><br>(OATP1B1/3 inhibition CYP3A inhibition, CYP2C9 induction) | Letermovir may increase the plasma concentrations of glyburide.<br><br>Frequent monitoring of glucose concentrations is recommended the first 2 weeks after initiating or ending letermovir, as well as after changing route of administration of letermovir.<br><br>When PREVYMIS is co-administered with cyclosporine, refer also to the glyburide prescribing information for specific dosing recommendations. |

| Concomitant medicinal product | Effect on concentration† Mean ratio (90 % confidence interval) for AUC, $C_{max}$ (likely mechanism of action) | Recommendations concerning co-administration with PREVYMIS |
|---|---|---|
| **Antiepileptic medicinal products (see also general text)** | | |
| carbamazepine, phenobarbital | Interaction not studied.<br>Expected:<br>↓ letermovir<br><br>(P-gp/UGT induction) | Carbamazepine or phenobarbital may decrease plasma concentrations of letermovir.<br>Co-administration of PREVYMIS and carbamazepine or phenobarbital is not recommended. |
| phenytoin | Interaction not studied.<br>Expected:<br>↓ letermovir<br><br>(P-gp/UGT induction)<br><br>↓ phenytoin<br><br>(CYP2C9/19 induction) | Phenytoin may decrease plasma concentrations of letermovir.<br><br>Letermovir may decrease the plasma concentrations of phenytoin.<br><br>Co-administration of PREVYMIS and phenytoin is not recommended. |
| **Oral anticoagulants** | | |
| warfarin | Interaction not studied.<br>Expected:<br>↓ warfarin<br><br>(CYP2C9 induction) | Letermovir may decrease the plasma concentrations of warfarin.<br><br>Frequent monitoring of International Normalised Ratio (INR) should be performed when warfarin is co-administered with PREVYMIS treatment#.<br>Monitoring is recommended the first 2 weeks after initiating or ending letermovir, as well as after changing route of administration of letermovir or immunosuppressant. |
| dabigatran | Interaction not studied.<br>Expected:<br>↓ dabigatran<br><br>(intestinal P-gp induction) | Letermovir may decrease the plasma concentrations of dabigatran and may decrease efficacy of dabigatran.<br>Concomitant use of dabigatran should be avoided due to the risk of reduced dabigatran efficacy.<br><br>When PREVYMIS is co-administered with cyclosporine, dabigatran is contraindicated. |

| Concomitant medicinal product | Effect on concentration† Mean ratio (90 % confidence interval) for AUC, $C_{max}$ (likely mechanism of action) | Recommendations concerning co-administration with PREVYMIS |
|---|---|---|
| **Sedatives** | | |
| midazolam (1 mg single dose IV)/ letermovir (240 mg once daily PO)<br><br>midazolam (2 mg single dose PO) / letermovir (240 mg once daily PO) | ↑ midazolam<br>IV:<br>AUC 1.47 (1.37, 1.58)<br>$C_{max}$ 1.05 (0.94, 1.17)<br><br>PO:<br>AUC 2.25 (2.04, 2.48)<br>$C_{max}$ 1.72 (1.55, 1.92)<br><br>(CYP3A inhibition) | Close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised during co-administration of PREVYMIS with midazolam. Dose adjustment of midazolam should be considered#. The increase in midazolam plasma concentration may be greater when oral midazolam is administered with letermovir at the clinical dose than with the dose studied. |
| **Opioid agonists** | | |
| Examples: alfentanil, fentanyl | Interaction not studied.<br>Expected:<br>↑ CYP3A metabolised opioids<br><br>(CYP3A inhibition) | Frequent monitoring for adverse reactions related to these medicinal products is recommended during co-administration. Dose adjustment of CYP3A metabolised opioids may be needed# (see section 4.4). Monitoring is also recommended if changing route of administration. When PREVYMIS is co-administered with cyclosporine, the magnitude of the increase in plasma concentrations of CYP3A metabolised opioids may be greater. Close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised during co-administration of PREVYMIS in combination with cyclosporine and alfentanil or fentanyl. Refer to the respective prescribing information (see section 4.4). |
| **Anti-arrhythmic medicinal products** | | |
| amiodarone | Interaction not studied.<br>Expected:<br>↑ amiodarone<br><br>(primarily CYP3A inhibition and CYP2C8 inhibition or induction) | Letermovir may increase the plasma concentrations of amiodarone.<br><br>Frequent monitoring for adverse reactions related to amiodarone is recommended during co-administration. Monitoring of amiodarone concentrations should be performed regularly when amiodarone is co-administered with PREVYMIS#. |
| quinidine | Interaction not studied.<br>Expected:<br>↑ quinidine<br><br>(CYP3A inhibition) | Letermovir may increase the plasma concentrations of quinidine.<br><br>Close clinical monitoring should be exercised during administration of PREVYMIS with quinidine. Refer to the respective prescribing information#. |

| Concomitant medicinal product | Effect on concentration† Mean ratio (90 % confidence interval) for AUC, $C_{max}$ (likely mechanism of action) | Recommendations concerning co-administration with PREVYMIS |
|---|---|---|
| **Cardiovascular medicinal products** | | |
| digoxin‡ (0.5 mg single dose)/ letermovir (240 mg twice daily) | ↔ digoxin<br>AUC 0.88 (0.80, 0.96)<br>$C_{max}$ 0.75 (0.63, 0.89)<br><br>(P-gp induction) | No dose adjustment required. |
| **Proton pump inhibitors** | | |
| omeprazole | Interaction not studied.<br>Expected:<br>↓omeprazole<br><br>(induction of CYP2C19)<br><br>Interaction not studied.<br>Expected:<br>↔ letermovir | Letermovir may decrease the plasma concentrations of CYP2C19 substrates.<br><br>Clinical monitoring and dose adjustment may be needed. |
| pantoprazole | Interaction not studied.<br>Expected:<br>↓ pantoprazole<br><br>(likely due to induction of CYP2C19)<br><br>Interaction not studied.<br>Expected:<br>↔ letermovir | Letermovir may decrease the plasma concentrations of CYP2C19 substrates.<br><br>Clinical monitoring and dose adjustment may be needed. |
| **Wakefulness-promoting agents** | | |
| modafinil | Interaction not studied.<br>Expected:<br>↓ letermovir<br><br>(P-gp/UGT induction) | Modafinil may decrease plasma concentrations of letermovir.<br>Co-administration of PREVYMIS and modafinil is not recommended. |

*This table is not all inclusive.
† ↓ =decrease, ↑ =increase
↔ =no clinically relevant change
‡ One-way interaction study assessing the effect of letermovir on the concomitant medicinal product.
§ These data are the effect of rifampicin on letermovir 24 hours after final rifampicin dose.
#Refer to the respective prescribing information.

Paediatric population
Interaction studies have only been performed in adults.

### 4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of letermovir in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).
PREVYMIS is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding
It is unknown whether letermovir is excreted in human milk.
Available pharmacodynamic/toxicological data in animals have shown excretion of letermovir in milk (see section 5.3).
A risk to the newborns/infants cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from PREVYMIS therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
There were no effects on female fertility in rats. Irreversible testicular toxicity and impairment of fertility was observed in male rats, but not in male mice or male monkeys.

## 4.7 Effects on ability to drive and use machines

PREVYMIS may have minor influence on the ability to drive or use machines. Fatigue and vertigo have been reported in some patients during treatment with PREVYMIS, which may influence a patient's ability to drive and use machines (see section 4.8).

## 4.8 Undesirable effects

Summary of the safety profile
The safety assessment of PREVYMIS was based on a Phase 3 clinical trial (P001) in HSCT recipients who received PREVYMIS or placebo through Week 14 post-transplant and were followed for safety through Week 24 post-transplant (see section 5.1).
The most commonly reported adverse reactions occurring in at least 1% of subjects in the PREVYMIS group and at a frequency greater than placebo were: nausea (7.2%), diarrhoea (2.4%), and vomiting (1.9%).
The most frequently reported adverse reactions that led to discontinuation of PREVYMIS were nausea (1.6%), vomiting (0.8%), and abdominal pain (0.5%).

Tabulated summary of adverse reactions
The following adverse reactions were identified in patients taking PREVYMIS in clinical trials. The adverse reactions are listed below by body system organ class and frequency. Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) or very rare (< 1/10,000).

**Table 2: Adverse reactions identified with PREVYMIS**

| Frequency | Adverse reactions |
|---|---|
| *Immune system disorders* | |
| Uncommon | hypersensitivity |
| *Metabolism and nutrition disorders* | |
| Uncommon | decreased appetite |
| *Nervous system disorders* | |
| Uncommon | dysgeusia, headache |
| *Ear and labyrinth disorders* | |
| Uncommon | vertigo |
| *Gastrointestinal disorders* | |
| Common | nausea, diarrhoea, vomiting |
| Uncommon | abdominal pain |
| *Hepatobiliary disorders* | |
| Uncommon | alanine aminotransferase increased, aspartate aminotransferase increased |
| *Musculoskeletal and connective tissue disorders* | |
| Uncommon | muscle spasms |
| *Renal and urinary disorders* | |
| Uncommon | blood creatinine increased |
| *General disorders and administration site conditions* | |
| Uncommon | fatigue, oedema peripheral |

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

There is no experience with human overdose with PREVYMIS. During Phase 1 clinical trials, 86 healthy subjects received doses ranging from 720 mg/day to 1440 mg/day of PREVYMIS for up to 14 days. The adverse reaction profile was similar to that of the clinical dose of 480 mg/day. There is no specific antidote for overdose with PREVYMIS. In case of overdose, it is recommended that the patient be monitored for adverse reactions and appropriate symptomatic treatment instituted.

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

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

Mechanism of action
Letermovir inhibits the CMV DNA terminase complex which is required for cleavage and packaging of viral progeny DNA. 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).

Viral resistance

*In cell culture*
The CMV genes UL51, UL56, and UL89 encode subunits of CMV DNA terminase. CMV mutants with reduced susceptibility to letermovir have been confirmed in cell culture. $EC_{50}$ values for recombinant CMV mutants expressing the substitutions map to pUL51 (P91S), pUL56 (C25F, S229F, V231A, V231L, V236A, T244K, T244R, L254F, L257F, L257I, F261C, F261L, F261S, Y321C, L328V, M329T, A365S, N368D), and pUL89 (N320H, D344E) were 1.6- to <10-fold higher than those for wild-type reference virus; these substitutions are not likely to be clinically relevant. $EC_{50}$ values for recombinant CMV mutants expressing pUL56 substitutions N232Y, V236L, V236M, E237D, E237G, L241P, K258E, C325F, C325R, C325W, C325Y, R369G, R369M, R369S and R369T were 10- to 9,300-fold higher than those for the wild-type reference virus; some of these substitutions have been observed in patients who have experienced prophylaxis failure in clinical studies (see below).

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

In a Phase 3 trial (P001), DNA sequence analysis of the entire coding regions of UL56 and UL89 was performed on samples obtained from 40 letermovir-treated subjects in the FAS population who experienced prophylaxis failure and for whom samples were available for analysis. Two subjects had letermovir-resistant GVs detected, both with substitutions mapping to pUL56. One subject had the substitution V236M and the other subject had the substitution E237G. One additional subject, who had detectable CMV DNA at baseline (and was therefore not in the FAS population), had pUL56 substitutions, C325W and R369T, detected after discontinuing letermovir.

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

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

Clinical efficacy and safety

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

were monitored through Week 24 post-transplant for the primary efficacy endpoint with continued follow-up through Week 48 post-transplant.

Subjects received CMV DNA monitoring weekly until post-transplant week 14 and then bi-weekly until post-transplant week 24, with initiation of standard-of-care CMV pre-emptive therapy if CMV DNAemia was considered clinically significant. Subjects had continued follow-up through Week 48 post-transplant.

Among the 565 treated subjects, 373 subjects received letermovir (including 99 subjects who received at least one IV dose) and 192 received placebo (including 48 subjects who received at least one IV dose). The median time to starting letermovir was 9 days after transplantation. Thirty-seven percent (37%) of subjects were engrafted at baseline. The median age was 54 years (range: 18 to 78 years); 56 (15.0%) subjects were 65 years of age or older: 58% were male; 82% were White; 10% were Asian; 2% were Black or African; and 7% were Hispanic or Latino. At baseline, 50% of subjects received a myeloablative regimen, 52% were receiving cyclosporine, and 42% were receiving tacrolimus. The most common primary reasons for transplant were acute myeloid leukemia (38%), myeloblastic syndrome (15%), and lymphoma (13%). Twelve percent (12%) of subjects were positive for CMV DNA at baseline.

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.

*Primary efficacy endpoint*
The primary efficacy endpoint of clinically significant CMV infection in P001 was defined by the incidence of CMV DNAemia warranting anti-CMV pre-emptive therapy (PET) or the occurrence of CMV end-organ disease. 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.
Letermovir demonstrated superior efficacy over placebo in the analysis of the primary endpoint, as shown in Table 3. The estimated treatment difference of -23.5% was statistically significant (one-sided p-value <0.0001).

**Table 3**: **P001: Efficacy results in HSCT recipients (NC=F Approach, FAS Population)**

| Parameter | Letermovir (N=325) n (%) | Placebo (N=170) n (%) |
|---|---|---|
| Primary efficacy endpoint (Proportion of subjects who failed prophylaxis by Week 24) | 122 (37.5) | 103 (60.6) |
| Reasons for Failures[†] | | |
| Clinically significant CMV infection | 57 (17.5) | 71 (41.8) |
| CMV DNAemia warranting anti-CMV PET | 52 (16.0) | 68 (40.0) |
| CMV end-organ disease | 5 (1.5) | 3 (1.8) |
| Discontinued from study | 56 (17.2) | 27 (15.9) |
| Missing outcome | 9 (2.8) | 5 (2.9) |
| Stratum-adjusted treatment difference (Letermovir-Placebo)[§] | | |
| Difference (95% CI) | -23.5 (-32.5, -14.6) | |
| p-value | <0.0001 | |

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

[§] 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.

FAS=Full analysis set; FAS includes randomised subjects who received at least one dose of study medicine, 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 with clinically significant CMV infection or who prematurely discontinued from the study or had a missing outcome through Week 24 post-transplant visit window.

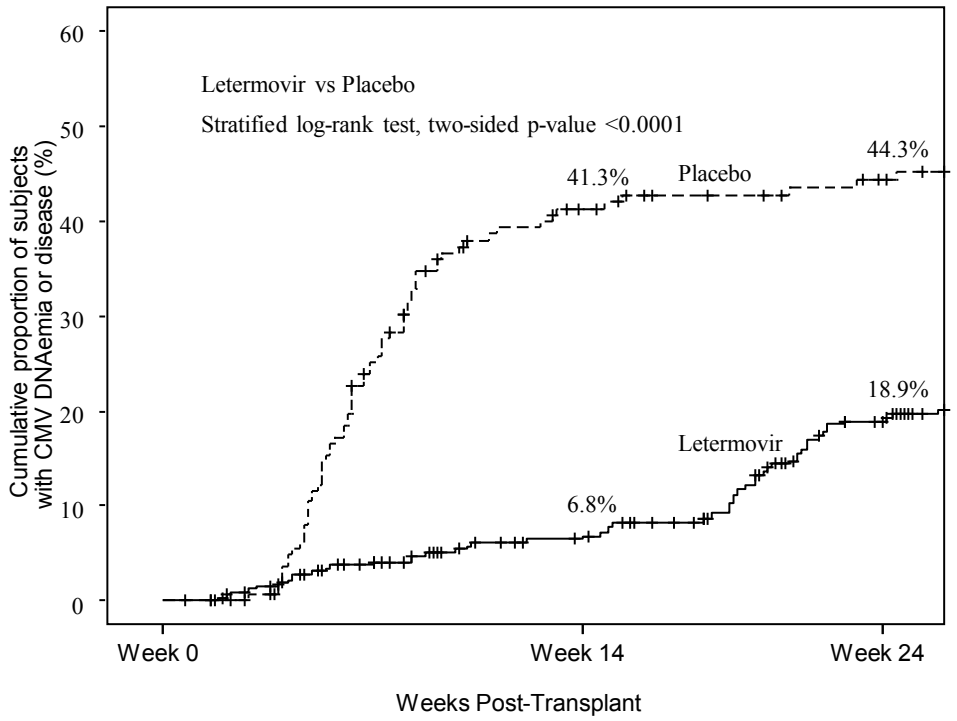
N = number of subjects in each treatment group.

n (%) = Number (percent) of subjects in each sub-category.

Note: The proportion of subjects with detectable CMV viral DNA on Day 1 that developed clinically significant CMV infection in the letermovir group was 64.6% (31/48) compared to 90.9% (20/22) in the placebo group through Week 24 post-transplant. The estimated difference (95% CI for the difference) was -26.1% (-45.9%, -6.3%), with a nominal one-sided p-value <0.0048.

Factors associated with CMV DNAemia after Week 14 post-transplant among letermovir-treated subjects included high risk for CMV reactivation at baseline, GVHD, use of corticosteroids, and CMV negative donor serostatus.

**Figure 1: P001: Kaplan-Meier plot of time to initiation of anti-CMV PET or onset of CMV end-organ disease through Week 24 post-transplant in HSCT recipients (FAS population)**

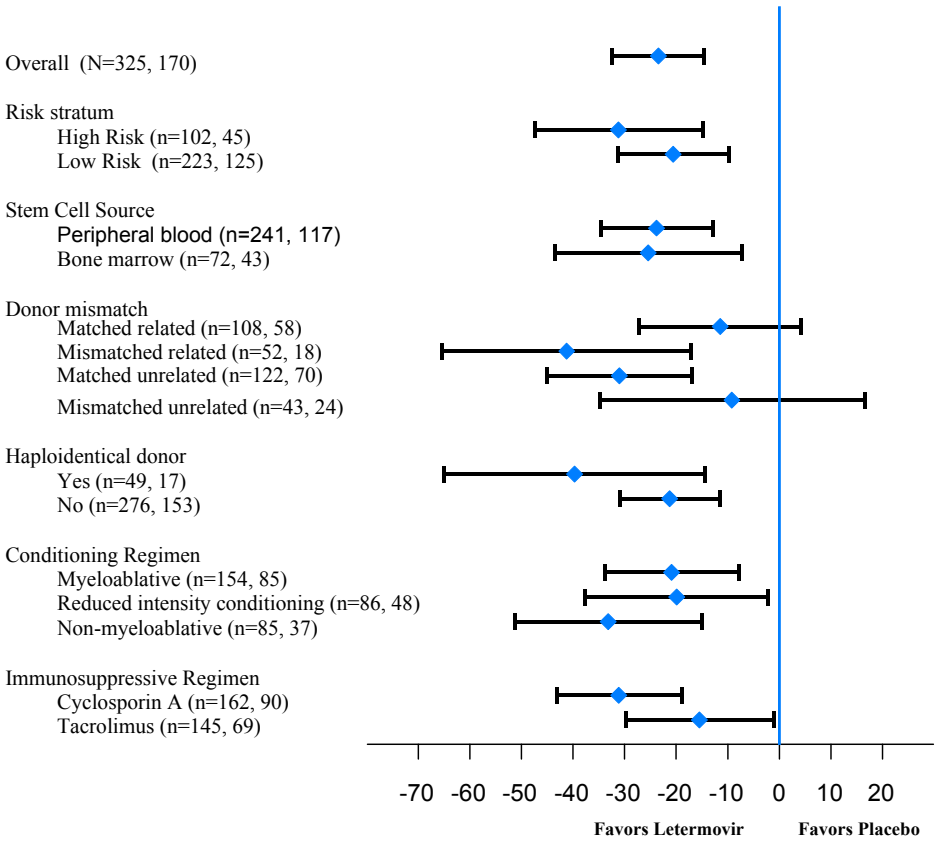



| Number of Subjects at Risk | | | |
|---|---|---|---|
| Letermovir | 325 | 270 | 212 |
| Placebo | 170 | 85 | 70 |

There were no differences in the incidence of or time to engraftment between the PREVYMIS and placebo groups.

Efficacy consistently favoured letermovir across subgroups including low and high risk for CMV reactivation, conditioning regimens, and concomitant immunosuppressive regimens (see Figure 2).

**Figure 2: P001: Forest plot of the proportion of subjects initiating anti-CMV PET or with CMV end-organ disease through Week 24 post-transplant by selected subgroups (NC=F approach, FAS population)**




NC=F, Non-Completer=Failure. With NC=F approach, 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.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with PREVYMIS in one or more subsets of the paediatric population for prophylaxis of cytomegalovirus infection (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

The pharmacokinetics of letermovir have been characterized following oral and IV administration in healthy subjects and HSCT recipients. Letermovir exposure increased in a greater than dose-proportional manner with both oral or IV administration. The mechanism is likely saturation/autoinhibition of OATP1B1/3.

In healthy subjects, 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 letermovir.

Letermovir reached steady-state in 9 to 10 days with an accumulation ratio of 1.2 for AUC and 1.0 for $C_{max}$.

In HSCT recipients, letermovir AUC was estimated using population pharmacokinetic analyses using Phase 3 data (see Table 4). Differences in exposure across treatment regimens are not clinically relevant; efficacy was consistent across the range of exposures observed in P001.

**Table 4: Letermovir AUC (ng•hr/mL) values in HSCT Recipients**

| Treatment Regimen | Median (90% Prediction Interval)* |
|---|---|
| 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) |
| * Population post-hoc predictions from the population PK analysis using Phase 3 data | |

Absorption

Letermovir was absorbed rapidly with a median time to maximum plasma concentration ($T_{max}$) of 1.5 to 3.0 hours and declined in a biphasic manner. In HSCT recipients, bioavailability of letermovir was estimated to be approximately 35% with 480 mg once daily oral letermovir 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 due to inhibition of OATP1B. Bioavailability of letermovir was estimated to be approximately 85% with 240 mg once daily oral letermovir co-administered with cyclosporine in patients.
If letermovir is co-administered with cyclosporine, the recommended dose of letermovir is 240 mg once daily (see section 4.2).

*Effect of food*

In healthy subjects, oral administration of 480 mg single dose of letermovir with a standard high fat and high calorie meal did not have any effect on the overall exposure (AUC) and resulted in approximately 30% increase in peak levels ($C_{max}$) of letermovir. Letermovir may be administered orally with or without food as has been done in the clinical studies (see section 4.2).

Distribution

Based on population pharmacokinetic analyses, the mean steady-state volume of distribution is estimated to be 45.5 L following intravenous administration in HSCT recipients.
Letermovir is extensively bound (98.2%) to human plasma proteins, independent of the concentration range (3 to 100 mg/L) evaluated, *in vitro*. Some saturation was observed at lower concentrations. Blood to plasma partitioning of letermovir is 0.56 and independent of the concentration range (0.1 to 10 mg/L) evaluated *in vitro*.
In preclinical distribution studies, letermovir is distributed to organs and tissues with the highest concentrations observed in the gastrointestinal tract, bile duct and liver and low concentrations in the brain.

Biotransformation

The majority of letermovir-related components 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 letermovir in healthy subjects. The major elimination pathways of letermovir is biliary excretion as well as direct glucuronidation. The process involves the hepatic uptake transporters OATP1B1 and 3 followed by UGT1A1/3 catalysed glucuronidation.

Based on population pharmacokinetic analyses, letermovir steady-state apparent CL is estimated to be 4.84 L/hr following intravenous administration of 480 mg in HSCT recipients. The inter-individual variability for CL is estimated to be 24.6%.

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

Pharmacokinetics in special populations

*Hepatic impairment*
Letermovir unbound AUC was approximately 81%- and 4-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.

Marked increases in letermovir unbound exposure are anticipated in patients with moderate hepatic impairment combined with moderate or severe renal impairment (see section 4.2).

*Renal impairment*
Letermovir unbound AUC was approximately 115- and 81% higher in subjects with moderate (eGFR of 31.0 to 56.8 mL/min/1.73m$^2$) and severe (eGFR of 11.9 to 28.1 mL/min/1.73m$^2$) renal impairment, respectively, compared to healthy subjects. The changes in letermovir exposure due to moderate or severe renal impairment are not considered to be clinically relevant. Subjects with ESRD have not been studied.

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

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

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

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

## 5.3 Preclinical safety data

General toxicity
Irreversible 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. There was no testicular toxicity in rats at exposures (AUC) similar to the exposures in humans at the RHD. 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.

It is known that hydroxypropylbetadex can cause kidney vacuolation in rats when given intravenously at doses greater than 50 mg/kg/day. Vacuolation was noted in the kidneys of rats administered IV letermovir formulated with 1500 mg/kg/day of the cyclodextrin excipient hydroxypropylbetadex.

Carcinogenesis
Carcinogenicity studies with letermovir have not been conducted.

Mutagenesis
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.

Reproduction
*Fertility*
In the fertility and early embryonic development studies in the rat, there were no effects of letermovir on female fertility. 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 General toxicity).

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

Development
In rats, maternal toxicity (including decrease in body weight gain) was noted at 250 mg/kg/day (approximately 11-fold the AUC at the RHD); in the offspring, decreased foetal weight with delayed ossification, slightly oedematous foetuses, and increased incidence of shortened umbilical cords and of variations and malformations in the vertebrae, ribs, and pelvis were observed. No maternal or developmental effects were noted at the dose of 50 mg/kg/day (approximately 2.5-fold the AUC at the RHD).
In rabbits, maternal toxicity (including mortality and abortions) was noted at 225 mg/kg/day (approximately 2-fold the AUC at the RHD); in the offspring, an increased incidence of malformations and variations in the vertebrae and ribs were observed.
In the pre- and post-natal developmental study, letermovir was administered orally to pregnant rats. There was no developmental toxicity observed up to the highest exposure tested (2-fold the AUC at the RHD).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Hydroxypropylbetadex (cyclodextrin)
Sodium chloride
Sodium hydroxide (E524)
Water for injections

### 6.2 Incompatibilities

Incompatible medicinal products
PREVYMIS concentrate for solution for infusion 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.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Incompatible intravenous 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.

This medicinal product must not be used with other intravenous bags and infusion set materials except those mentioned in section 6.6.

**6.3. Shelf life**

Unopened vial: 30 months
After opening: Use immediately

Storage of diluted solution
Chemical and physical in-use stability has been demonstrated for 48 hours at 25 °C and for 48 hours at 2 to 8 °C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

**6.4 Special precautions for storage**

This medicinal product does not require any special temperature storage conditions. Store in original carton to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

**6.5 Nature and contents of container**

Type I (30 mL) clear glass vial with a 20 mm fluorocoated chlorobutyl stopper with aluminium flip-off cap containing 12 mL(medium green cap) or 24 mL (dark blue cap) of solution.
Pack size: 1 vial.

**6.6 Special precautions for disposal and other handling**

PREVYMIS vials are for single use only.

Preparation
The preparation and administration instructions are the same for either dose.
PREVYMIS concentrate for solution for infusion must be diluted prior to intravenous use.
Inspect vial contents for discolouration and particulate matter prior to dilution. PREVYMIS concentrate for solution for infusion is a clear, colourless solution and may contain a few product-related small translucent or white particles. Do not use the vial if the solution is cloudy, discoloured or contains matter other than a few small translucent or white particles.
Do not use PREVYMIS concentrate for solution for infusion with IV bags and infusion set materials containing polyurethane or the plasticizer diethylhexyl phthalate (DEHP). Materials that are phthalate-free are also DEHP-free.
Do not shake PREVYMIS vial.
Add one single-dose vial (either 12 mL (240 mg dose) or 24 mL (480 mg dose)) of PREVYMIS concentrate for solution for infusion to a 250 mL pre-filled IV bag containing either 0.9% sodium chloride or 5% dextrose, and mix the diluted solution by gentle inversion. Do not shake.
Once diluted, the solution of PREVYMIS is clear, and ranges from colourless to yellow. Variations of colour within this range do not affect the quality of the product. The diluted solution should be inspected visually for particulate matter and discolouration prior to administration. Discard if the diluted solution is cloudy, discoloured or contains matter other than a few small translucent or white

particles. If a vial is added to a 250 mL IV diluent bag, the final concentration ranges of letermovir would be 0.9 mg/mL (for 240 mg dose) and 1.8 mg/mL (for 480 mg dose).

Administration
See section 4.2.

PREVYMIS diluted solution must be administered through a sterile 0.2 micron or 0.22 micron polyethersulfone (PES) in-line filter.

Compatible intravenous solutions and other medicinal products
PREVYMIS concentrate for solution for infusion is compatible with 0.9% sodium chloride and 5% dextrose solutions.

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

**List of compatible medicinal products when PREVYMIS and medicinal products* are prepared in 0.9% sodium chloride**

- Ampicillin sodium
- Ampicillin sodium/Sulbactam sodium
- Anti-thymocyte globulin
- Caspofungin
- Daptomycin
- Fentanyl citrate
- Fluconazole
- Human insulin
- Magnesium sulfate
- Methotrexate
- Micafungin

*Refer to the prescribing information to confirm compatibility of simultaneous co-administration.

**List of compatible medicinal products when PREVYMIS and medicinal products* are prepared in 5% dextrose**

- 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

*Refer to the prescribing information to confirm compatibility of simultaneous co-administration.
[†]Amphotericin B (lipid complex) is compatible with PREVYMIS. However, Amphotericin B (liposomal) is incompatible (see section 6.2).

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

*Intravenous bag materials*
Polyvinyl chloride (PVC), ethylene vinyl acetate (EVA) and polyolefin (polypropylene and polyethylene)

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

*Plasticizers*
Tris (2-ethylhexyl) trimellitate (TOTM), butyl benzyl phthalate (BBP)

*Catheters*
Radiopaque polyurethane

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1245/003
EU/1/17/1245/004

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8 January 2018

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.