ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PREVYMIS 240 mg film-coated tablets
PREVYMIS 480 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PREVYMIS 240 mg film-coated tablets

Each film-coated tablet contains 240 mg of letermovir.

PREVYMIS 480 mg film-coated tablets

Each film-coated tablet contains 480 mg of letermovir.

Excipients with known effect

Each 240 mg film-coated tablet contains 4 mg of lactose (as monohydrate).
Each 480 mg film-coated tablet contains 6.4 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

PREVYMIS 240 mg film-coated tablets

Yellow oval tablet of dimensions 16.5 mm x 8.5 mm, debossed with "591" on one side and corporate logo on the other side.

PREVYMIS 480 mg film-coated tablets

Pink oval, bi-convex tablet of dimensions 21.2 mm x 10.3 mm, debossed with "595" on one side and corporate logo on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PREVYMIS is indicated for prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult and paediatric patients weighing at least 15 kg who are CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT).

PREVYMIS is indicated for prophylaxis of CMV disease in CMV-seronegative adult and paediatric patients weighing at least 40 kg who have received a kidney transplant from a CMV-seropositive donor [D+/R-].

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

4.2 Posology and method of administration

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

Posology

Letermovir is also available as granules in sachet (20 mg and 120 mg) and as concentrate for solution for infusion (240 mg and 480 mg).

Letermovir tablets, granules in sachet, and concentrate for solution for infusion may be used interchangeably at the discretion of the physician. Dose adjustment may be necessary for paediatric patients weighing less than 30 kg when switching between oral and intravenous formulations. Refer to the prescribing information for the letermovir concentrate for solution for infusion for dosing information.

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

Prolonged letermovir prophylaxis beyond 100 days post-HSCT may be of benefit in some patients at high risk for late CMV reactivation (see section 5.1). The safety and efficacy of letermovir use for more than 200 days has not been studied in clinical trials.

Adult and paediatric patients weighing at least 30 kg who are HSCT recipients
The recommended dose of letermovir is 480 mg once daily that can be administered either as one 480 mg tablet or as two 240 mg tablets.

For patients who cannot swallow tablets, refer to the prescribing information for the letermovir granules in sachet for dosing information.

Dose adjustment in adult and paediatric patients weighing at least 30 kg who are HSCT recipients
If letermovir is co-administered with cyclosporine, the dose of letermovir should be decreased to 240 mg once daily (see sections 4.5 and 5.2).

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

Paediatric patients weighing at least 15 kg to less than 30 kg who are HSCT recipients
The recommended dose of letermovir is 240 mg once daily that can be administered as one 240 mg tablet (see also section 5.2).

For paediatric patients who cannot swallow tablets, refer to the prescribing information for letermovir granules in sachet for dosing information.

Dose adjustment in paediatric patients weighing at least 15 kg to less than 30 kg who are HSCT recipients
If oral letermovir is co-administered with cyclosporine, the dose of letermovir should be decreased to 120 mg once daily (see also sections 4.5 and 5.2). For patients requiring a 120 mg dose, refer to the prescribing information for the letermovir granules in sachet for dosing information.

- If cyclosporine is initiated after starting letermovir, the next dose of letermovir should be decreased to 120 mg once daily.

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

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

Adult and paediatric patients weighing at least 40 kg who are kidney transplant recipients
The recommended dose of letermovir is 480 mg once daily that can be administered either as one 480 mg tablet or as two 240 mg tablets.

For patients who cannot swallow tablets, refer to the prescribing information for the letermovir granules in sachet for dosing information.

Dose adjustment in adult and paediatric patients weighing at least 40 kg who are kidney transplant recipients
If letermovir is co-administered with cyclosporine, the dose of letermovir should be decreased to 240 mg once daily (see sections 4.5 and 5.2).
- If cyclosporine is initiated after starting letermovir, the next dose of letermovir should be decreased to 240 mg once daily.
- If cyclosporine is discontinued after starting letermovir, the next dose of letermovir should be increased to 480 mg once daily.
- If cyclosporine dosing is temporarily interrupted due to high cyclosporine levels, no dose adjustment of letermovir is needed.

Missed dose
Patients should be instructed that if they miss a dose of letermovir, they should take it as soon as they remember. If they do not remember until it is time for the next dose, they should skip the missed dose and go back to the regular schedule. Patients should not double their next dose or take more than the prescribed dose.

Special populations

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

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

Combined hepatic and renal impairment
Letermovir 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 letermovir 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.

Paediatric population
The safety and efficacy of letermovir in HSCT patients weighing less than 5 kg or in kidney transplant patients weighing less than 40 kg have not been established. No data are available. No recommendation on posology for kidney transplant patients weighing less than 40 kg could be supported by pharmacokinetic/pharmacodynamic extrapolation.

Method of administration

For oral use.
The tablet should be swallowed whole and may be taken with or without food. The tablet should not be divided, crushed, or chewed because these methods have not been studied.

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 in HSCT recipients

In a Phase 3 trial (P001), the safety and efficacy of letermovir has been established in HSCT 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 every two weeks 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 letermovir 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

Letermovir 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).

Excipients

PREVYMIS contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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 metabolising enzymes or transporters

Co-administration of letermovir (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, 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 letermovir with medicinal products that are inhibitors of OATP1B1/3 transporters may result in increased letermovir plasma concentrations. If letermovir is co-administered with cyclosporine (a potent OATP1B1/3 inhibitor), the recommended dose of letermovir is 240 mg once daily in adult and paediatric patients weighing at least 30 kg (see Table 1 and sections 4.2 and 5.2). If oral letermovir is co-administered with cyclosporine in paediatric patients weighing less than 30 kg, the dose should be decreased (see 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 letermovir with oral midazolam (a CYP3A substrate) results in 2-3-fold increased midazolam plasma concentrations. Co-administration of letermovir 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 letermovir 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 intravenous than oral letermovir.
The magnitude of the OATP1B1/3 inhibition on co-administered medicinal products is likely greater when letermovir 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 letermovir 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 intravenous 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 letermovir 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 a 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.

General information

If dose adjustments of concomitant medicinal products are made due to treatment with letermovir, doses should be readjusted after treatment with letermovir 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 adult studies conducted with letermovir or are predicted medicinal product interactions that may occur with letermovir (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 in adults 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 intravenously, 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 letermovir**
Antibiotics		
nafcillin	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	Nafcillin may decrease plasma concentrations of letermovir. Co-administration of letermovir and nafcillin is not recommended.
Antifungals		
fluconazole (400 mg single dose)/letermovir (480 mg single dose)	↔ fluconazole AUC 1.03 (0.99, 1.08) C_{max} 0.95 (0.92, 0.99) ↔ letermovir AUC 1.11 (1.01, 1.23) C_{max} 1.06 (0.93, 1.21) Interaction at steady state not studied. Expected: ↔ fluconazole ↔ letermovir	No dose adjustment required.
itraconazole (200 mg once daily PO)/letermovir (480 mg once daily PO)	↔ itraconazole AUC 0.76 (0.71, 0.81) C_{max} 0.84 (0.76, 0.92) ↔ letermovir AUC 1.33 (1.17, 1.51) C_{max} 1.21 (1.05, 1.39)	No dose adjustment required.
posaconazole[‡] (300 mg single dose)/ letermovir (480 mg daily)	↔ posaconazole AUC 0.98 (0.82, 1.17) C_{max} 1.11 (0.95, 1.29)	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 letermovir**
voriconazole[‡] (200 mg twice daily)/ letermovir (480 mg daily)	↓ voriconazole AUC 0.56 (0.51, 0.62) C_{max} 0.61 (0.53, 0.71) (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.
Antimycobacterials		
rifabutin	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	Rifabutin may decrease plasma concentrations of letermovir. Co-administration of letermovir and rifabutin is not recommended.
rifampicin		Multiple dose rifampicin decreases plasma concentrations of letermovir. Co-administration of letermovir and rifampicin is not recommended.
(600 mg single dose PO)/ letermovir (480 mg single dose PO)	↔letermovir AUC 2.03 (1.84, 2.26) C_{max} 1.59 (1.46, 1.74) C_{24} 2.01 (1.59, 2.54) (OATP1B1/3 and/or P-gp inhibition)	
(600 mg single dose intravenous)/ letermovir (480 mg single dose PO)	↔ letermovir AUC 1.58 (1.38, 1.81) C_{max} 1.37 (1.16, 1.61) C_{24} 0.78 (0.65, 0.93) (OATP1B1/3 and/or P-gp inhibition)	
(600 mg once daily PO)/ letermovir (480 mg once daily PO)	↓ letermovir AUC 0.81 (0.67, 0.98) C_{max} 1.01 (0.79, 1.28) C_{24} 0.14 (0.11, 0.19) (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 AUC 0.15 (0.13, 0.17) C_{max} 0.27 (0.22, 0.31) C_{24} 0.09 (0.06, 0.12) (P-gp/UGT induction)	
Antipsychotics		
thioridazine	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	Thioridazine may decrease plasma concentrations of letermovir. Co-administration of letermovir and thioridazine is not recommended.
Endothelin antagonists		
bosentan	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	Bosentan may decrease plasma concentrations of letermovir. Co-administration of letermovir and bosentan is not recommended.

Concomitant medicinal product	Effect on concentration† mean ratio (90% confidence interval) for AUC, C_{max} (likely mechanism of action)	Recommendations concerning co-administration with letermovir
Antivirals		
acyclovir‡ (400 mg single dose)/ letermovir (480 mg daily)	↔ acyclovir AUC 1.02 (0.87, 1.2) C_{max} 0.82 (0.71, 0.93)	No dose adjustment required.
valacyclovir	Interaction not studied. Expected: ↔ valacyclovir	No dose adjustment required.
Herbal products		
St. John's wort (*Hypericum perforatum*)	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	St. John's wort may decrease plasma concentrations of letermovir. Co-administration of letermovir and St. John's wort is contraindicated.
HIV medicinal products		
efavirenz	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction) ↑ or ↓ efavirenz (CYP2B6 inhibition or induction)	Efavirenz may decrease plasma concentrations of letermovir. Co-administration of letermovir and efavirenz is not recommended.
etravirine, nevirapine, ritonavir, lopinavir	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	These antivirals may decrease plasma concentrations of letermovir. Co-administration of letermovir with these antivirals is not recommended.
HMG-CoA reductase inhibitors		
atorvastatin‡ (20 mg single dose)/ letermovir (480 mg daily)	↑ atorvastatin AUC 3.29 (2.84, 3.82) C_{max} 2.17 (1.76, 2.67) (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 letermovir #. Although not studied, when letermovir is co-administered with cyclosporine, the magnitude of the increase in atorvastatin plasma concentrations is expected to be greater than with letermovir alone. When letermovir is co-administered with cyclosporine, atorvastatin is contraindicated.
simvastatin, pitavastatin, rosuvastatin	Interaction not studied. Expected: ↑ HMG-CoA reductase inhibitors (CYP3A, OATP1B1/3 inhibition)	Letermovir may substantially increase plasma concentrations of these statins. Concomitant use is not recommended with letermovir alone. When letermovir 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 letermovir**
fluvastatin, pravastatin	Interaction not studied. Expected: ↑ HMG-CoA reductase inhibitors (OATP1B1/3 and/or BCRP inhibition)	Letermovir may increase statin plasma concentrations. When letermovir is co-administered with these statins, a statin dose reduction may be necessary[#]. Statin-associated adverse events such as myopathy should be closely monitored. When letermovir 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 AUC 1.66 (1.51, 1.82) C_{max} 1.08 (0.97, 1.19) (CYP3A inhibition)	If letermovir is co-administered with cyclosporine, the dose of letermovir should be decreased to 240 mg once daily in adults (see sections 4.2 and 5.1) and paediatric patients weighing at least 30 kg (see section 4.2). If oral letermovir is co-administered with cyclosporine in paediatric patients weighing less than 30 kg, the dose should be decreased (see section 4.2). Frequent monitoring of cyclosporine whole blood concentrations should be performed during treatment, when changing letermovir administration route, and at discontinuation of letermovir and the dose of cyclosporine adjusted accordingly[#].
cyclosporine (200 mg single dose)/ letermovir (240 mg daily)	↑ letermovir AUC 2.11 (1.97, 2.26) C_{max} 1.48 (1.33, 1.65) (OATP1B1/3 inhibition)	
mycophenolate mofetil (1 g single dose)/ letermovir (480 mg daily)	↔mycophenolic acid AUC 1.08 (0.97, 1.20) C_{max} 0.96 (0.82, 1.12) ↔ letermovir AUC 1.18 (1.04, 1.32) 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 letermovir
sirolimus‡ (2 mg single dose)/ letermovir (480 mg daily)	↑ sirolimus AUC 3.40 (3.01, 3.85) C_{max} 2.76 (2.48, 3.06) (CYP3A inhibition) Interaction not studied. Expected: ↔ letermovir	Frequent monitoring of sirolimus whole blood concentrations should be performed during treatment, when changing letermovir administration route, and at discontinuation of letermovir and the dose of sirolimus adjusted accordingly#. Frequent monitoring of sirolimus concentrations is recommended at initiation or discontinuation of cyclosporine co-administration with letermovir. When letermovir is co-administered with cyclosporine, also refer to the sirolimus prescribing information for specific dosing recommendations for use of sirolimus with cyclosporine. When letermovir is co-administered with cyclosporine, the magnitude of the increase in concentrations of sirolimus may be greater than with letermovir alone.
tacrolimus (5 mg single dose)/ letermovir (480 mg daily)	↑ tacrolimus AUC 2.42 (2.04, 2.88) C_{max} 1.57 (1.32, 1.86) (CYP3A inhibition)	Frequent monitoring of tacrolimus whole blood concentrations should be performed during treatment, when changing letermovir administration route, and at discontinuation of letermovir and the dose of tacrolimus adjusted accordingly#.
tacrolimus (5 mg single dose)/ letermovir (80 mg twice daily)	↔ letermovir AUC 1.02 (0.97, 1.07) 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 AUC 1.42 (1.32, 1.52) C_{max} 0.89 (0.83, 0.96) ↔ LNG AUC 1.36 (1.30, 1.43) 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. 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 letermovir
Antidiabetic medicinal products		
repaglinide	Interaction not studied. Expected: ↑ or ↓ repaglinide (CYP2C8 induction, CYP2C8 and OATP1B inhibition)	Letermovir may increase or decrease the plasma concentrations of repaglinide. (The net effect is not known). Concomitant use is not recommended. When letermovir 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. Expected: ↑ glyburide (OATP1B1/3 inhibition CYP3A inhibition, CYP2C9 induction)	Letermovir may increase the plasma concentrations of glyburide. 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. When letermovir is co-administered with cyclosporine, refer also to the glyburide prescribing information for specific dosing recommendations.
Antiepileptic medicinal products (see also general text)		
carbamazepine, phenobarbital	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	Carbamazepine or phenobarbital may decrease plasma concentrations of letermovir. Co-administration of letermovir and carbamazepine or phenobarbital is not recommended.
phenytoin	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction) ↓ phenytoin (CYP2C9/19 induction)	Phenytoin may decrease plasma concentrations of letermovir. Letermovir may decrease the plasma concentrations of phenytoin. Co-administration of letermovir and phenytoin is not recommended.

Concomitant medicinal product	Effect on concentration† mean ratio (90% confidence interval) for AUC, C_{max} (likely mechanism of action)	Recommendations concerning co-administration with letermovir
Oral anticoagulants		
warfarin	Interaction not studied. Expected: ↓ warfarin (CYP2C9 induction)	Letermovir may decrease the plasma concentrations of warfarin. Frequent monitoring of International Normalised Ratio (INR) should be performed when warfarin is co-administered with letermovir treatment#. 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. Expected: ↓ dabigatran (intestinal P-gp induction)	Letermovir may decrease the plasma concentrations of dabigatran and may decrease efficacy of dabigatran. Concomitant use of dabigatran should be avoided due to the risk of reduced dabigatran efficacy. When letermovir is co-administered with cyclosporine, dabigatran is contraindicated.
Sedatives		
midazolam (1 mg single dose intravenous)/ letermovir (240 mg once daily PO) midazolam (2 mg single dose PO) / letermovir (240 mg once daily PO)	↑ midazolam Intravenous: AUC 1.47 (1.37, 1.58) C_{max} 1.05 (0.94, 1.17) PO: AUC 2.25 (2.04, 2.48) C_{max} 1.72 (1.55, 1.92) (CYP3A inhibition)	Close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised during co-administration of letermovir 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. Expected: ↑ CYP3A metabolised opioids (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 letermovir 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 letermovir in combination with cyclosporine and alfentanil or fentanyl. Refer to the

Concomitant medicinal product	Effect on concentration† mean ratio (90% confidence interval) for AUC, C_{max} (likely mechanism of action)	Recommendations concerning co-administration with letermovir
		respective prescribing information (see section 4.4).
Anti-arrhythmic medicinal products		
amiodarone	Interaction not studied. Expected: ↑ amiodarone (primarily CYP3A inhibition and CYP2C8 inhibition or induction)	Letermovir may increase the plasma concentrations of amiodarone. 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 letermovir#.
quinidine	Interaction not studied. Expected: ↑ quinidine (CYP3A inhibition)	Letermovir may increase the plasma concentrations of quinidine. Close clinical monitoring should be exercised during administration of letermovir with quinidine. Refer to the respective prescribing information#.
Cardiovascular medicinal products		
digoxin‡ (0.5 mg single dose)/ letermovir (240 mg twice daily)	↔ digoxin AUC 0.88 (0.80, 0.96) C_{max} 0.75 (0.63, 0.89) (P-gp induction)	No dose adjustment required.
Proton pump inhibitors		
omeprazole	Interaction not studied. Expected: ↓omeprazole (induction of CYP2C19) Interaction not studied. Expected: ↔ letermovir	Letermovir may decrease the plasma concentrations of CYP2C19 substrates. Clinical monitoring and dose adjustment may be needed.
pantoprazole	Interaction not studied. Expected: ↓ pantoprazole (likely due to induction of CYP2C19) Interaction not studied. Expected: ↔ letermovir	Letermovir may decrease the plasma concentrations of CYP2C19 substrates. Clinical monitoring and dose adjustment may be needed.

Concomitant medicinal product	Effect on concentration† mean ratio (90% confidence interval) for AUC, C_{max} (likely mechanism of action)	Recommendations concerning co-administration with letermovir
Wakefulness-promoting agents		
modafinil	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	Modafinil may decrease plasma concentrations of letermovir. Co-administration of letermovir 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).

Letermovir 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 letermovir 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 (see section 5.3).

4.7 Effects on ability to drive and use machines

Letermovir may have minor influence on the ability to drive or use machines. Fatigue and vertigo have been reported in some patients during treatment with letermovir, 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 letermovir was based on three Phase 3 clinical trials.

HSCT
In P001, 565 adult HSCT recipients received letermovir 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 letermovir 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 letermovir were: nausea (1.6%), vomiting (0.8%), and abdominal pain (0.5%).

In P040, 218 adult HSCT recipients received letermovir or placebo from Week 14 (~100 days) through Week 28 (~200 days) post-HSCT and were followed for safety through Week 48 post-HSCT (see section 5.1). The adverse reactions reported were consistent with the safety profile of letermovir as characterised in study P001.

Kidney transplant
In P002, 292 adult kidney transplant recipients received letermovir through Week 28 (~200 days) post-transplant (see section 5.1).

Tabulated summary of adverse reactions

The following adverse reactions were identified in adult patients taking letermovir 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 letermovir

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

Paediatric population

The safety assessment of letermovir in paediatric patients from birth up to 18 years old was based on a Phase 2b clinical trial (P030). In P030, 63 HSCT recipients were treated with letermovir through Week 14 post-HSCT. Their age distribution was as follows, i.e., 28 adolescents, 14 children aged 7 to less than 12 years, 13 aged 2 to less than 7 years, and 8 less than 2 years old (5 of them less than 1 year old). The adverse reactions were consistent with those observed in clinical studies of letermovir in adults.

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 letermovir. During Phase 1 clinical trials, 86 healthy adult subjects received doses ranging from 720 mg/day to 1 440 mg/day of letermovir 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 letermovir. 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 letermovir 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 pUL51 substitution A95V or 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 trials (see below).

In clinical trials
In a Phase 2b trial evaluating letermovir doses of 60, 120, or 240 mg/day or placebo for up to 84 days in 131 adult 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 adult 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.

In a Phase 3 trial (P040), DNA sequence analysis of the entire coding regions of UL51, UL56 and UL89 was performed on samples obtained from 32 adult subjects (regardless of treatment group) who experienced prophylaxis failure or who discontinued early with CMV viremia. There were no letermovir resistance-associated substitutions detected above the validated assay limit of 5%.

In a Phase 3 trial (P002), DNA sequence analysis of the entire coding regions of UL51, UL56 and UL89 was performed on samples obtained from 52 letermovir-treated adult subjects who experienced CMV disease or who discontinued early with CMV viremia. There were no letermovir resistance-associated substitutions detected above the validated assay limit of 5%.

In a Phase 2b trial (P030), DNA sequence analysis of the entire coding regions of UL51, UL56 and UL89 was performed on samples obtained from 10 letermovir-treated paediatric subjects at a visit for evaluation of CMV infection. A total of 2 letermovir resistance-associated substitutions both mapping to pUL56 were detected in 2 subjects. One subject had the substitution R369S and the other subject had the substitution C325W.

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 intravenously 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 adult subjects. Letermovir does not prolong QTc to any clinically relevant extent following the 960 mg intravenous dose with plasma concentrations approximately 2-fold higher than the 480 mg intravenous dose.

Clinical efficacy and safety

Adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant

P001: Prophylaxis through Week 14 (~100 days) post-HSCT
To evaluate letermovir prophylaxis as a preventive strategy for CMV infection or disease, the efficacy of letermovir was assessed in a multicentre, 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-HSCT) and continued through Week 14 post-HSCT. Letermovir was administered either orally or intravenously; the dose of letermovir was the same regardless of the route of administration. Subjects were monitored through Week 24 post-HSCT for the primary efficacy endpoint with continued follow-up through Week 48 post-HSCT.

Subjects received CMV DNA monitoring weekly until post-HSCT week 14 and then every two weeks until post-HSCT 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-HSCT.

Among the 565 treated subjects, 373 subjects received letermovir (including 99 subjects who received at least one intravenous dose) and 192 received placebo (including 48 subjects who received at least one intravenous 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 leukaemia (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 Leucocyte 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-HSCT or had a missing outcome at Week 24 post-HSCT 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).

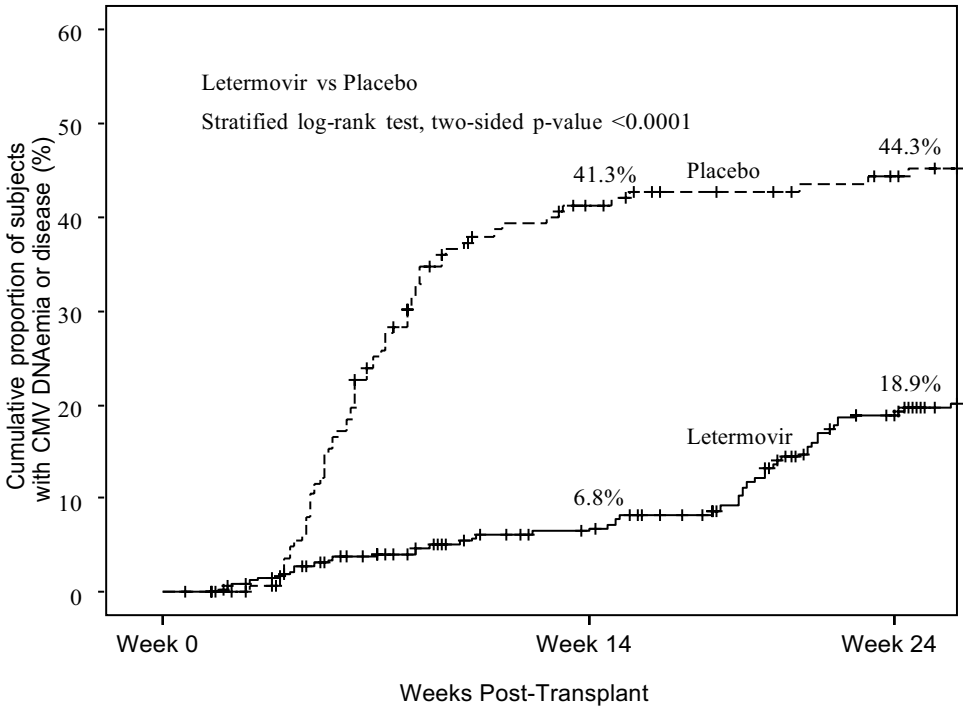
Table 3: P001: Efficacy results in HSCT recipients (NC=F Approach, FAS Population)

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-HSCT 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-HSCT. The estimated difference (95% CI for the difference) was -26.1% (-45.9%, -6.3%), with a nominal one-sided p-value < 0.0048.

Factors associated with CMV DNAemia after Week 14 post-HSCT 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)

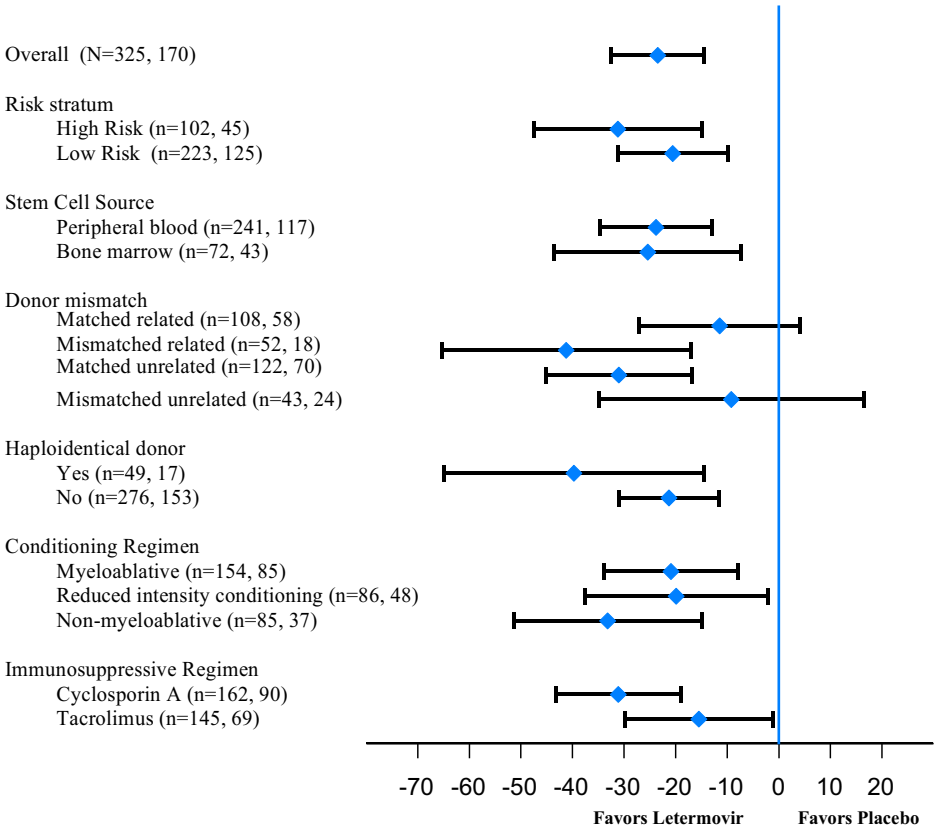


Number of Subjects at Risk			
Letermovir	325	270	212
Placebo	170	85	70

There were no differences in the incidence of or time to engraftment between the letermovir 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-HSCT 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.

P040: Prophylaxis from Week 14 (~100 days) through Week 28 (~200 days) post-HSCT
The efficacy of extending letermovir prophylaxis from Week 14 (~100 days) through Week 28 (~200 days) post-HSCT in patients at risk for late CMV infection and disease was assessed in a multicentre, double-blind, placebo-controlled Phase 3 trial (P040) in adult CMV-seropositive recipients [R+] of an allogeneic HSCT. Eligible subjects who completed letermovir prophylaxis through ~100 days post-HSCT were randomised (2:1) to receive letermovir or placebo from Week 14 through Week 28 post-HSCT. Subjects were monitored through Week 28 post-HSCT for the primary efficacy endpoint with continued off-treatment follow-up through Week 48 post-HSCT.

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

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

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

Letermovir demonstrated superior efficacy over placebo in the analysis of the primary endpoint, as shown in Table 4. The estimated treatment difference of -16.1% was statistically significant (one-sided p-value=0.0005). Efficacy consistently favored letermovir across subgroups based on subject characteristics (age, gender, race) and risk factors for late CMV infection and disease.

Table 4: P040: Efficacy results in HSCT recipients at risk for late CMV infection and disease (OF approach, FAS population)

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

* The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.
† Clinically significant CMV infection was defined as CMV end-organ disease (proven or probable) or initiation of PET based on documented CMV viremia and the clinical condition of the subject.
‡ 95% CIs and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (haploidentical donor yes or no). A one-sided p-value ≤0.0249 was used for declaring statistical significance.
Approach to handling missing values: Observed Failure (OF) approach. With the OF approach, failure was defined as all subjects who developed clinically significant CMV infection or discontinued prematurely from the study with CMV viremia from Week 14 (~100 days) through Week 28 (~200 days) post-HSCT.
N=Number of subjects in each treatment group.
n (%)=Number (percent) of subjects in each sub-category.

P002: *Adult CMV-seronegative recipients of a kidney transplant from a CMV-seropositive donor [D+/R-]*
To evaluate letermovir prophylaxis as a preventive strategy for CMV disease in kidney transplant recipients, the efficacy of letermovir was assessed in a multicentre, double-blind, active comparator-controlled non-inferiority Phase 3 trial (P002) in adult kidney transplant recipients at high risk [D+/R-]. Subjects were randomised (1:1) to receive either letermovir or valganciclovir. Letermovir was given concomitantly with acyclovir. Valganciclovir was given concomitantly with a placebo to acyclovir. Randomisation was stratified by the use or non-use of highly cytolytic, anti-lymphocyte immunotherapy during induction. Letermovir or valganciclovir were initiated between Day 0 and Day

7 post-kidney transplant and continued through Week 28 (~200 days) post-transplant. Subjects were monitored through Week 52 post-transplant.

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

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

Letermovir demonstrated non-inferiority to valganciclovir in the analysis of the primary endpoint, as shown in Table 5.

Table 5: P002: Efficacy results in kidney transplant recipients (OF approach, FAS population)

Parameter	Letermovir (N=289) n (%)	Valganciclovir (N=297) n (%)
CMV disease* through Week 52	**30 (10.4)**	**35 (11.8)**
Stratum-adjusted treatment difference (Letermovir-Valganciclovir)[†] Difference (95% CI)	-1.4 (-6.5, 3.8)[‡]	
* CMV disease cases confirmed by an independent adjudication committee. [†] The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (use/non-use of highly cytolytic, anti-lymphocyte immunotherapy during induction). [‡] Based on a non-inferiority margin of 10%, letermovir is non-inferior to valganciclovir. Approach to handling missing values: Observed Failure (OF) approach. With OF approach, participants who discontinue prematurely from the study for any reason are not considered failures. Note: Subjects randomised to the letermovir group were given acyclovir for herpes simplex virus (HSV) and varicella zoster virus (VZV) prophylaxis. Subjects randomised to the valganciclovir group were given a placebo to acyclovir. N=number of subjects in each treatment group. n (%)=Number (percent) of subjects in each sub-category.		

Efficacy was comparable across all subgroups, including sex, age, race, region, and the use/non-use of highly cytolytic, anti-lymphocyte immunotherapy during induction.

Paediatric population

P030: *Paediatric recipients of an allogeneic hematopoietic stem cell transplant*
To evaluate letermovir prophylaxis as a preventive strategy for CMV infection or disease in paediatric transplant recipients, the efficacy of letermovir was assessed in a multicentre, open-label, single-arm Phase 2b trial (P030) in paediatric recipients of an allogeneic HSCT. Study drug was initiated after HSCT (Day 0-28 post-HSCT) and continued through Week 14 post-HSCT. Study drug was administered either orally or intravenously; the dose of letermovir was based on age, body weight and formulation.

Among the 63 treated subjects, 8 were 0 to less than 2 years of age, 27 were 2 to less than 12 years of age and 28 were 12 to less than 18 years of age. At baseline, 87% of subjects received a myeloablative regimen, 67% were receiving cyclosporine, and 27% were receiving tacrolimus. The most common

primary reasons for transplant were acute myeloid leukaemia (18%) and aplastic anaemia (10%) in the overall population, and combined immunodeficiency (37.5%) and familial haemophagocytic lymphohistiocytosis (25.0%) in children less than 2 years of age.

Secondary efficacy endpoint
The efficacy endpoints of P030 were secondary and included the incidence of clinically significant CMV infection through Week 14 post-HSCT and through Week 24 post-HSCT. Clinically significant CMV infection was defined as the occurrence of either CMV end-organ disease, or initiation of anti-CMV PET based on documented CMV viremia and the clinical condition of the subject. The incidence of clinically significant CMV infection was 7.1% and 10.7% through Week 14 post-HSCT and Week 24 post-HSCT, respectively.

5.2 Pharmacokinetic properties

In healthy adult subjects, the pharmacokinetics of letermovir have been characterised following oral and intravenous administration. Letermovir exposure increased in a greater than dose-proportional manner with both oral or intravenous administration. The mechanism is likely saturation/autoinhibition of OATP1B1/3. The pharmacokinetics of letermovir have also been characterised following oral and intravenous administration in adult HSCT recipients (see Table 6) and paediatric HSCT recipients (see Table 8 and Table 9) and following oral administration in adult kidney transplant recipients (see Table 7).

Healthy adult 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 for C_{max}.

Adult HSCT recipients
Letermovir AUC was estimated using population pharmacokinetic analyses using P001 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 adult HSCT Recipients

Treatment Regimen	Median (90% Prediction Interval)*
480 mg Oral, no cyclosporine	34 400 (16 900, 73 700)
480 mg intravenous, no cyclosporine	100 000 (65 300, 148 000)
240 mg Oral, with cyclosporine	60 800 (28 700, 122 000)
240 mg intravenous, with cyclosporine	70 300 (46 200, 106 000)
* Population post-hoc predictions from the population PK analysis using Phase 3 data	

Adult kidney transplant recipients
Letermovir AUC was estimated using population pharmacokinetic analysis using P002 Phase 3 data (see Table 7). Efficacy was consistent across the range of exposures observed in P002.

Table 7: Letermovir AUC (ng•hr/mL) values in adult kidney transplant recipients

Treatment Regimen	Median (90% Prediction Interval)*
480 mg Oral, no cyclosporine	62 200 (28 900, 145 000)
240 mg Oral, with cyclosporine	57 700 (26 900, 135 000)
* Medians and 90% prediction intervals are based on simulations using the Phase 3 population PK model with inter-individual variability. Note: PK of letermovir was not studied following intravenous administration in kidney transplant recipients; however, the projected AUC following intravenous administration is similar to the model predicted AUC following intravenous administration in HSCT recipients (see Table 6).	

Absorption

In healthy adult subjects, 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 adult 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%. In adult kidney transplant recipients, bioavailability of letermovir was estimated to be approximately 60% with 480 mg once daily oral letermovir administered without cyclosporine.

Effect of cyclosporine
In adult 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 in adult and paediatric patients weighing at least 30 kg (see section 4.2). If oral letermovir is co-administered with cyclosporine in paediatric patients weighing less than 30 kg, the dose should be decreased (see section 4.2).

Effect of food
In healthy adult subjects, oral administration of 480 mg single dose of letermovir tablet 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 tablets may be administered orally with or without food as has been done in the clinical trials (see section 4.2).

In healthy adult subjects, oral administration of 240 mg single dose of letermovir granules with soft foods (pudding or applesauce) resulted in an approximately 13% and 20% increase in overall exposure (AUC) and resulted in approximately 25% and 33% increase in peak levels (C_{max}) of letermovir. Letermovir granules may be administered with soft foods, as has been done in the paediatric trial (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 adult 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 intravenous letermovir in healthy adult 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 adult 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 adult 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 adult subjects. The changes in letermovir exposure in adult 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
Clinical study in a renally impaired population
Letermovir unbound AUC was approximately 115- and 81% higher in adult 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 adult 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.

Post-kidney transplant (P002)
Based on population pharmacokinetic analysis, letermovir AUC was approximately 12%, 27% and 35% higher in adult subjects with mild (CrCl greater than or equal to 60 to less than 90 mL/min), moderate (CrCl greater than or equal to 30 to less than 60 mL/min) and severe (CrCl greater than or equal to 15 to less than 30 mL/min) renal impairment, respectively, compared to adult subjects with CrCl greater than or equal to 90 mL/min. These changes are not considered to be clinically relevant.

Weight
Based on population pharmacokinetic analyses in healthy adult subjects, letermovir AUC is estimated to be 18.7% lower in subjects weighing 80-100 kg compared to subjects weighing 67 kg. Based on population pharmacokinetic analysis in adult kidney transplant recipients (P002), letermovir AUC is estimated to be 26% lower in subjects weighing greater than 80 kg compared to subjects weighing less than or equal to 80 kg. These differences are not clinically relevant.

Race
Based on population pharmacokinetic analyses in healthy adult subjects, 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 adult 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.

Paediatric population
Letermovir AUC in paediatric HSCT recipients was estimated via population pharmacokinetic analysis using observed PK data from study P030 (see Table 8 and Table 9). Exposures for paediatric HSCT recipients across body weight bands are within the range of exposures achieved in the adult HSCT reference exposures (see Table 6).

Table 8: Letermovir AUC (ng•hr/mL) values following oral administration in paediatric HSCT recipients

Body weight	Oral dose, no cyclosporine	Median (90% prediction interval)*	Oral dose, with cyclosporine	Median (90% prediction interval)*
30 kg and above	480 mg	39 100 (18 700-81 300)	240 mg	49 100 (23 200-104 000)
15 kg to less than 30 kg	240 mg	38 900 (20 200-74 300)	120 mg	51 000 (26 600-98 200)
7.5 kg to less than 15 kg	120 mg	32 000 (16 700-59 300)	60 mg	41 600 (22 300-81 100)
5 kg to less than 7.5 kg	80 mg	30 600 (16 200-55 000)	40 mg	39 000 (20 600-72 000)
* Medians and 90% prediction intervals are based on simulations using the paediatric HSCT population PK model with inter-individual variability.				

Table 9: Letermovir AUC (ng•hr/mL) values following intravenous administration in paediatric HSCT recipients

Body weight	Intravenous dose, no cyclosporine	Median (90% prediction interval)*	Intravenous dose, with cyclosporine	Median (90% prediction interval)*
30 kg and above	480 mg	111 000 (55 700-218 000)	240 mg	59 800 (28 400-120 000)
15 kg to less than 30 kg	120 mg	57 200 (29 700-113 000)	120 mg	61 100 (29 900-121 000)
7.5 kg to less than 15 kg	60 mg	46 000 (24 300-83 900)	60 mg	49 200 (25 800-93 800)
5 kg to less than 7.5 kg	40 mg	43 400 (24 300-81 000)	40 mg	45 900 (24 900-82 200)
* Medians and 90% prediction intervals are based on simulations using the paediatric HSCT population PK model with inter-individual variability.				

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 characterised 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.

Carcinogenesis

A 6-month oral carcinogenicity study in RasH2 transgenic (Tg.RasH2) mice showed no evidence of human-relevant tumorigenesis up to the highest doses tested, 150 mg/kg/day and 300 mg/kg/day in males and females, respectively.

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

Tablet core

Microcrystalline cellulose (E460)
Croscarmellose sodium (E468)
Povidone (E1201)
Colloidal anhydrous silica (E551)
Magnesium stearate (E470b)

Film-coating

Lactose monohydrate
Hypromellose (E464)
Titanium dioxide (E171)
Triacetin
Iron oxide yellow (E172)
Iron oxide red (only for 480 mg tablets) (E172)
Carnauba wax (E903)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Packs of 28x1 tablets in Polyamide/Aluminium/PVC – Aluminium perforated unit dose blisters.

6.6 Special precautions for disposal

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/1/17/1245/001
EU/1/17/1245/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8 January 2018
Date of latest renewal: 24 August 2022

10. DATE OF REVISION OF THE TEXT

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

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.

Excipients with known effect

This medicinal product contains 23 mg (1 mmol) sodium per 240 mg vial.
This medicinal product contains 46 mg (2 mmol) sodium per 480 mg vial.

This medicinal product contains 1 800 mg hydroxypropylbetadex (cyclodextrin) per 240 mg vial.
This medicinal product contains 3 600 mg hydroxypropylbetadex (cyclodextrin) per 480 mg vial.

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 and paediatric patients weighing at least 5 kg who are CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT).

PREVYMIS is indicated for prophylaxis of CMV disease in CMV-seronegative adult and paediatric patients weighing at least 40 kg who have received a kidney transplant from a CMV-seropositive donor [D+/R-].

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

4.2 Posology and method of administration

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

Posology

Letermovir is also available for oral administration (240 mg and 480 mg film-coated tablets, and 20 mg and 120 mg granules in sachet).

Letermovir tablets, granules in sachet, and concentrate for solution for infusion may be used interchangeably at the discretion of the physician. Dose adjustment may be necessary for paediatric patients weighing less than 30 kg when switching between oral and intravenous formulations. Refer to the prescribing information for the letermovir film-coated tablets or letermovir granules in sachet for dosing information.

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

Prolonged letermovir prophylaxis beyond 100 days post-HSCT may be of benefit in some patients at high risk for late CMV reactivation (see section 5.1). The safety and efficacy of letermovir use for more than 200 days has not been studied in clinical trials.

Adult and paediatric patients weighing at least 30 kg who are HSCT recipients
The recommended dose of letermovir is 480 mg once daily.

Dose adjustment in adult and paediatric patients weighing at least 30 kg who are HSCT recipients
If letermovir is co-administered with cyclosporine, the dose of letermovir should be decreased to 240 mg once daily (see sections 4.5 and 5.2).

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

Paediatric patients weighing less than 30 kg who are HSCT recipients
The recommended doses of letermovir for paediatric patients weighing less than 30 kg are shown in Table 1 (see also section 5.2). Letermovir should be administered once daily.

Dose adjustment in paediatric patients weighing less than 30 kg who are HSCT recipients
If intravenous letermovir is co-administered with cyclosporine, the dose of letermovir does not require adjustment as shown in Table 1 (see also sections 4.5 and 5.2).

Table 1: Recommended dose of letermovir concentrate for solution for infusion without or with cyclosporine in paediatric patients weighing less than 30 kg

Body weight	Daily intravenous dose without or with cyclosporine
15 kg to less than 30 kg	120 mg
7.5 kg to less than 15 kg	60 mg
5 kg to less than 7.5 kg	40 mg

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

Adult and paediatric patients weighing at least 40 kg who are kidney transplant recipients
The recommended dose of letermovir is 480 mg once daily.

Dose adjustment in adult and paediatric patients weighing at least 40 kg who are kidney transplant recipients
If letermovir is co-administered with cyclosporine, the dose of letermovir should be decreased to 240 mg once daily (see sections 4.5 and 5.2).

- If cyclosporine is initiated after starting letermovir, the next dose of letermovir should be decreased to 240 mg once daily.
- If cyclosporine is discontinued after starting letermovir, the next dose of letermovir should be increased to 480 mg once daily.
- If cyclosporine dosing is temporarily interrupted due to high cyclosporine levels, no dose adjustment of letermovir 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 letermovir is required based on age (see sections 5.1 and 5.2).

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

Combined hepatic and renal impairment
Letermovir 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 letermovir 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 (see sections 4.4 and 5.3). In patients with moderate or severe renal impairment (creatinine clearance less than 50 mL/min), or in young children (less than 2 years of age) receiving PREVYMIS, accumulation of hydroxypropylbetadex could occur. Serum creatinine levels should be closely monitored in these patients.

Paediatric population
If possible, intravenous administration should not exceed 4 weeks.

The safety and efficacy of letermovir in HSCT patients weighing less than 5 kg or in kidney transplant patients weighing less than 40 kg have not been established. No data are available. No recommendation on posology for kidney transplant patients weighing less than 40 kg could be supported by pharmacokinetic/pharmacodynamic extrapolation.

Method of administration

For intravenous use only.

Letermovir concentrate for solution for infusion requires dilution (see section 6.6) prior to administration.

Letermovir 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.

Letermovir should be administered as an intravenous infusion only.

After dilution, letermovir 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 intravenous 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 in HSCT recipients

In a Phase 3 trial (P001), the safety and efficacy of letermovir has been established in HSCT 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 every two weeks 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 letermovir 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 2 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

Letermovir 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 2).

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

Sodium

This medicinal product contains 23 mg (or 1 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 should be taken into consideration by patients on a controlled sodium diet.

This medicinal product contains 46 mg (or 2 mmol) sodium per 480 mg vial, equivalent to 2.30% of the WHO recommended maximum daily intake of 2 g sodium for an adult. This should be taken into consideration by patients on a controlled sodium diet.

Cyclodextrin

This medicinal product contains 300 mg hydroxypropylbetadex (cyclodextrin) per 40 mg dose.
This medicinal product contains 450 mg hydroxypropylbetadex (cyclodextrin) per 60 mg dose.
This medicinal product contains 900 mg hydroxypropylbetadex (cyclodextrin) per 120 mg dose.
This medicinal product contains 1 800 mg hydroxypropylbetadex (cyclodextrin) per 240 mg dose.
This medicinal product contains 3 600 mg hydroxypropylbetadex (cyclodextrin) per 480 mg dose.

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 2).

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 metabolising enzymes or transporters

Co-administration of letermovir (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 2).

-Examples of strong inducers include rifampicin, phenytoin, carbamazepine, 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 2).

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

Inhibitors of OATP1B1 or 3
Co-administration of letermovir with medicinal products that are inhibitors of OATP1B1/3 transporters may result in increased letermovir plasma concentrations. If letermovir is co-administered with cyclosporine (a potent OATP1B1/3 inhibitor), the recommended dose of letermovir is 240 mg once daily in adult and paediatric patients weighing at least 30 kg (see Table 2 and sections 4.2 and 5.2). If intravenous letermovir is co-administered with cyclosporine in paediatric patients weighing less than 30 kg, dose adjustment is not required (see Table 2 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 letermovir with oral midazolam (a CYP3A substrate) results in 2-3-fold increased midazolam plasma concentrations. Co-administration of letermovir 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 2). 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 letermovir 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 2). Comparing letermovir regimen administered without cyclosporine, the effect is more marked after intravenous than oral letermovir.
The magnitude of the OATP1B1/3 inhibition on co-administered medicinal products is likely greater when letermovir 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 letermovir 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 2).
The effect is expected to be less pronounced for oral letermovir without cyclosporine, than intravenous 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 2). 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 letermovir 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 a 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.

General information

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

Table 2 provides a listing of established or potentially clinically significant medicinal product interactions. The medicinal product interactions described are based on adult studies conducted with letermovir or are predicted medicinal product interactions that may occur with letermovir (see sections 4.3, 4.4, 5.1, and 5.2).

Table 2: 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 in adults 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 intravenously, 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 letermovir**
Antibiotics		
nafcillin	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	Nafcillin may decrease plasma concentrations of letermovir. Co-administration of letermovir and nafcillin is not recommended.

Concomitant medicinal product	Effect on concentration† mean ratio (90% confidence interval) for AUC, C_{max} (likely mechanism of action)	Recommendations concerning co-administration with letermovir
Antifungals		
fluconazole (400 mg single dose)/letermovir (480 mg single dose)	↔ fluconazole AUC 1.03 (0.99, 1.08) C_{max} 0.95 (0.92, 0.99) ↔ letermovir AUC 1.11 (1.01, 1.23) C_{max} 1.06 (0.93, 1.21) Interaction at steady state not studied. Expected: ↔ fluconazole ↔ letermovir	No dose adjustment required.
itraconazole (200 mg once daily PO)/letermovir (480 mg once daily PO)	↔ itraconazole AUC 0.76 (0.71, 0.81) C_{max} 0.84 (0.76, 0.92) ↔ letermovir AUC 1.33 (1.17, 1.51) C_{max} 1.21 (1.05, 1.39)	No dose adjustment required.
posaconazole‡ (300 mg single dose)/ letermovir (480 mg daily)	↔ posaconazole AUC 0.98 (0.82, 1.17) C_{max} 1.11 (0.95, 1.29)	No dose adjustment required.
voriconazole‡ (200 mg twice daily)/ letermovir (480 mg daily)	↓ voriconazole AUC 0.56 (0.51, 0.62) C_{max} 0.61 (0.53, 0.71) (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.
Antimycobacterials		
rifabutin	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	Rifabutin may decrease plasma concentrations of letermovir. Co-administration of letermovir and rifabutin is not recommended.
rifampicin		Multiple dose rifampicin decreases plasma concentrations of letermovir. Co-administration of letermovir and rifampicin is not recommended.
(600 mg single dose PO)/ letermovir (480 mg single dose PO)	↔ letermovir AUC 2.03 (1.84, 2.26) C_{max} 1.59 (1.46, 1.74) C_{24} 2.01 (1.59, 2.54) (OATP1B1/3 and/or P-gp inhibition)	
(600 mg single dose intravenous)/ letermovir (480 mg single dose PO)	↔ letermovir AUC 1.58 (1.38, 1.81) C_{max} 1.37 (1.16, 1.61) C_{24} 0.78 (0.65, 0.93) (OATP1B1/3 and/or P-gp inhibition)	

Concomitant medicinal product	**Effect on concentration[†] mean ratio (90% confidence interval) for AUC, C_{max} (likely mechanism of action)**	**Recommendations concerning co-administration with letermovir**
(600 mg once daily PO)/ letermovir (480 mg once daily PO)	↓ letermovir AUC 0.81 (0.67, 0.98) C_{max} 1.01 (0.79, 1.28) C_{24} 0.14 (0.11, 0.19) (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 AUC 0.15 (0.13, 0.17) C_{max} 0.27 (0.22, 0.31) C_{24} 0.09(0.06, 0.12) (P-gp/UGT induction)	
Antipsychotics		
thioridazine	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	Thioridazine may decrease plasma concentrations of letermovir. Co-administration of letermovir and thioridazine is not recommended.
Endothelin antagonists		
bosentan	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	Bosentan may decrease plasma concentrations of letermovir. Co-administration of letermovir and bosentan is not recommended.
Antivirals		
acyclovir[‡] (400 mg single dose)/ letermovir (480 mg daily)	↔ acyclovir AUC 1.02 (0.87, 1.2) C_{max} 0.82 (0.71, 0.93)	No dose adjustment required.
valacyclovir	Interaction not studied. Expected: ↔ valacyclovir	No dose adjustment required.
Herbal products		
St. John's wort (*Hypericum perforatum*)	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	St. John's wort may decrease plasma concentrations of letermovir. Co-administration of letermovir and St. John's wort is contraindicated.
HIV medicinal products		
efavirenz	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction) ↑ or ↓ efavirenz (CYP2B6 inhibition or induction)	Efavirenz may decrease plasma concentrations of letermovir. Co-administration of letermovir and efavirenz is not recommended.

Concomitant medicinal product	Effect on concentration† mean ratio (90% confidence interval) for AUC, C_{max} (likely mechanism of action)	Recommendations concerning co-administration with letermovir
etravirine, nevirapine, ritonavir, lopinavir	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	These antivirals may decrease plasma concentrations of letermovir. Co-administration of letermovir with these antivirals is not recommended.
HMG-CoA reductase inhibitors		
atorvastatin‡ (20 mg single dose)/ letermovir (480 mg daily)	↑ atorvastatin AUC 3.29 (2.84, 3.82) C_{max} 2.17 (1.76, 2.67) (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 letermovir#. Although not studied, when letermovir is co-administered with cyclosporine, the magnitude of the increase in atorvastatin plasma concentrations is expected to be greater than with letermovir alone. When letermovir is co-administered with cyclosporine, atorvastatin is contraindicated.
simvastatin, pitavastatin, rosuvastatin	Interaction not studied. Expected: ↑ HMG-CoA reductase inhibitors (CYP3A, OATP1B1/3 inhibition)	Letermovir may substantially increase plasma concentrations of these statins. Concomitant use is not recommended with letermovir alone. When letermovir is co-administered with cyclosporine, use of these statins is contraindicated.
fluvastatin, pravastatin	Interaction not studied. Expected: ↑ HMG-CoA reductase inhibitors (OATP1B1/3 and/or BCRP inhibition)	Letermovir may increase statin plasma concentrations. When letermovir is co-administered with these statins, a statin dose reduction may be necessary#. Statin-associated adverse events such as myopathy should be closely monitored. When letermovir 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.

Concomitant medicinal product	Effect on concentration† mean ratio (90% confidence interval) for AUC, C_{max} (likely mechanism of action)	Recommendations concerning co-administration with letermovir
Immunosuppressants		
cyclosporine (50 mg single dose)/ letermovir (240 mg daily)	↑ cyclosporine AUC 1.66 (1.51, 1.82) C_{max} 1.08 (0.97, 1.19) (CYP3A inhibition)	If letermovir is co-administered with cyclosporine, the dose of letermovir should be decreased to 240 mg once daily in adults (see sections 4.2 and 5.1) and paediatric patients weighing at least 30 kg (see section 4.2). If intravenous letermovir is co-administered with cyclosporine in paediatric patients weighing less than 30 kg, dose adjustment is not required (see section 4.2). Frequent monitoring of cyclosporine whole blood concentrations should be performed during treatment, when changing letermovir administration route, and at discontinuation of letermovir and the dose of cyclosporine adjusted accordingly#.
cyclosporine (200 mg single dose)/ letermovir (240 mg daily)	↑ letermovir AUC 2.11 (1.97, 2.26) C_{max} 1.48 (1.33, 1.65) (OATP1B1/3 inhibition)	
mycophenolate mofetil (1 g single dose)/ letermovir (480 mg daily)	↔mycophenolic acid AUC 1.08 (0.97, 1.20) C_{max} 0.96 (0.82, 1.12) ↔ letermovir AUC 1.18 (1.04, 1.32) C_{max} 1.11 (0.92, 1.34)	No dose adjustment required.
sirolimus‡ (2 mg single dose)/ letermovir (480 mg daily)	↑ sirolimus AUC 3.40 (3.01, 3.85) C_{max} 2.76 (2.48, 3.06) (CYP3A inhibition) Interaction not studied. Expected: ↔ letermovir	Frequent monitoring of sirolimus whole blood concentrations should be performed during treatment, when changing letermovir administration route, and at discontinuation of letermovir and the dose of sirolimus adjusted accordingly#. Frequent monitoring of sirolimus concentrations is recommended at initiation or discontinuation of cyclosporine co-administration with letermovir. When letermovir is co-administered with cyclosporine, also refer to the sirolimus prescribing information for specific dosing recommendations for use of sirolimus with cyclosporine. When letermovir is co-administered with cyclosporine, the magnitude of the increase in concentrations of sirolimus may be greater than with letermovir alone.
tacrolimus (5 mg single dose)/ letermovir (480 mg daily)	↑ tacrolimus AUC 2.42 (2.04, 2.88) C_{max} 1.57 (1.32, 1.86) (CYP3A inhibition)	Frequent monitoring of tacrolimus whole blood concentrations should be performed during treatment, when changing letermovir administration route, and at

Concomitant medicinal product	**Effect on concentration[†] mean ratio (90% confidence interval) for AUC, C_{max} (likely mechanism of action)**	**Recommendations concerning co-administration with letermovir**
tacrolimus (5 mg single dose)/ letermovir (80 mg twice daily)	↔ letermovir AUC 1.02 (0.97, 1.07) C_{max} 0.92 (0.84, 1.00)	discontinuation of letermovir and the dose of tacrolimus adjusted accordingly[#].
Oral contraceptives		
ethinylestradiol (EE) (0.03 mg)/ levonorgestrel (LNG)[‡] (0.15 mg) single dose/ letermovir (480 mg daily)	↔ EE AUC 1.42 (1.32, 1.52) C_{max} 0.89 (0.83, 0.96) ↔ LNG AUC 1.36 (1.30, 1.43) 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. For adequate contraceptive effect to be ensured with an oral contraceptive, products containing EE and LNG should be chosen.
Antidiabetic medicinal products		
repaglinide	Interaction not studied. Expected: ↑ or ↓ repaglinide (CYP2C8 induction, CYP2C8 and OATP1B inhibition)	Letermovir may increase or decrease the plasma concentrations of repaglinide. (The net effect is not known). Concomitant use is not recommended. When letermovir 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. Expected: ↑ glyburide (OATP1B1/3 inhibition CYP3A inhibition, CYP2C9 induction)	Letermovir may increase the plasma concentrations of glyburide. 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. When letermovir 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 letermovir
Antiepileptic medicinal products (see also general text)		
carbamazepine, phenobarbital	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	Carbamazepine or phenobarbital may decrease plasma concentrations of letermovir. Co-administration of letermovir and carbamazepine or phenobarbital is not recommended.
phenytoin	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction) ↓ phenytoin (CYP2C9/19 induction)	Phenytoin may decrease plasma concentrations of letermovir. Letermovir may decrease the plasma concentrations of phenytoin. Co-administration of letermovir and phenytoin is not recommended.
Oral anticoagulants		
warfarin	Interaction not studied. Expected: ↓ warfarin (CYP2C9 induction)	Letermovir may decrease the plasma concentrations of warfarin. Frequent monitoring of International Normalised Ratio (INR) should be performed when warfarin is co-administered with letermovir treatment[#]. 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. Expected: ↓ dabigatran (intestinal P-gp induction)	Letermovir may decrease the plasma concentrations of dabigatran and may decrease efficacy of dabigatran. Concomitant use of dabigatran should be avoided due to the risk of reduced dabigatran efficacy. When letermovir is co-administered with cyclosporine, dabigatran is contraindicated.
Sedatives		
midazolam (1 mg single dose intravenous)/ letermovir (240 mg once daily PO) midazolam (2 mg single dose PO) / letermovir (240 mg once daily PO)	↑ midazolam Intravenous: AUC 1.47 (1.37, 1.58) C_{max} 1.05 (0.94, 1.17) PO: AUC 2.25 (2.04, 2.48) C_{max} 1.72 (1.55, 1.92) (CYP3A inhibition)	Close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised during co-administration of letermovir 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.

Concomitant medicinal product	Effect on concentration† mean ratio (90% confidence interval) for AUC, C_{max} (likely mechanism of action)	Recommendations concerning co-administration with letermovir
Opioid agonists		
Examples: alfentanil, fentanyl	Interaction not studied. Expected: ↑ CYP3A metabolised opioids (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 letermovir 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 letermovir 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. Expected: ↑ amiodarone (primarily CYP3A inhibition and CYP2C8 inhibition or induction)	Letermovir may increase the plasma concentrations of amiodarone. 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 letermovir#.
quinidine	Interaction not studied. Expected: ↑ quinidine (CYP3A inhibition)	Letermovir may increase the plasma concentrations of quinidine. Close clinical monitoring should be exercised during administration of letermovir with quinidine. Refer to the respective prescribing information#.
Cardiovascular medicinal products		
digoxin‡ (0.5 mg single dose)/ letermovir (240 mg twice daily)	↔ digoxin AUC 0.88 (0.80, 0.96) C_{max} 0.75 (0.63, 0.89) (P-gp induction)	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 letermovir
Proton pump inhibitors		
omeprazole	Interaction not studied. Expected: ↓omeprazole (induction of CYP2C19) Interaction not studied. Expected: ↔ letermovir	Letermovir may decrease the plasma concentrations of CYP2C19 substrates. Clinical monitoring and dose adjustment may be needed.
pantoprazole	Interaction not studied. Expected: ↓ pantoprazole (likely due to induction of CYP2C19) Interaction not studied. Expected: ↔ letermovir	Letermovir may decrease the plasma concentrations of CYP2C19 substrates. Clinical monitoring and dose adjustment may be needed.
Wakefulness-promoting agents		
modafinil	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	Modafinil may decrease plasma concentrations of letermovir. Co-administration of letermovir 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).

Letermovir 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 letermovir 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 (see section 5.3).

4.7 Effects on ability to drive and use machines

Letermovir may have minor influence on the ability to drive or use machines. Fatigue and vertigo have been reported in some patients during treatment with letermovir, 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 letermovir was based on three Phase 3 clinical trials.

HSCT
In P001, 565 adult HSCT recipients received letermovir 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 letermovir 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 letermovir were: nausea (1.6%), vomiting (0.8%), and abdominal pain (0.5%).

In P040, 218 adult HSCT recipients received letermovir or placebo from Week 14 (~100 days) through Week 28 (~200 days) post-HSCT and were followed for safety through Week 48 post-HSCT (see section 5.1). The adverse reactions reported were consistent with the safety profile of letermovir as characterised in study P001.

Kidney transplant
In P002, 292 adult kidney transplant recipients received letermovir through Week 28 (~200 days) post-transplant (see section 5.1).

Tabulated summary of adverse reactions

The following adverse reactions were identified in adult patients taking letermovir 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 3: Adverse reactions identified with letermovir

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

Paediatric population

The safety assessment of letermovir in paediatric patients from birth up to 18 years old was based on a Phase 2b clinical trial (P030). In P030, 63 HSCT recipients were treated with letermovir through Week 14 post-HSCT. Their age distribution was as follows, i.e., 28 adolescents, 14 children aged 7 to less than 12 years, 13 aged 2 to less than 7 years, and 8 less than 2 years old (5 of them less than 1 year old). The adverse reactions were consistent with those observed in clinical studies of letermovir in adults.

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 letermovir. During Phase 1 clinical trials, 86 healthy adult subjects received doses ranging from 720 mg/day to 1 440 mg/day of letermovir 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 letermovir. 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 letermovir 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 pUL51 substitution A95V or 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 trials (see below).

In clinical trials
In a Phase 2b trial evaluating letermovir doses of 60, 120, or 240 mg/day or placebo for up to 84 days in 131 adult 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 adult 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.

In a Phase 3 trial (P040), DNA sequence analysis of the entire coding regions of UL51, UL56 and UL89 was performed on samples obtained from 32 adult subjects (regardless of treatment group) who experienced prophylaxis failure or who discontinued early with CMV viremia. There were no letermovir resistance-associated substitutions detected above the validated assay limit of 5%.

In a Phase 3 trial (P002), DNA sequence analysis of the entire coding regions of UL51, UL56 and UL89 was performed on samples obtained from 52 letermovir-treated adult subjects who experienced CMV disease or who discontinued early with CMV viremia. There were no letermovir resistance-associated substitutions detected above the validated assay limit of 5%.

In a Phase 2b trial (P030), DNA sequence analysis of the entire coding regions of UL51, UL56 and UL89 was performed on samples obtained from 10 letermovir-treated paediatric subjects at a visit for evaluation of CMV infection. A total of 2 letermovir resistance-associated substitutions both mapping to pUL56 were detected in 2 subjects. One subject had the substitution R369S and the other subject had the substitution C325W.

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 intravenously 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 adult subjects. Letermovir does not prolong QTc to any clinically relevant extent following the 960 mg intravenous dose with plasma concentrations approximately 2-fold higher than the 480 mg intravenous dose.

Clinical efficacy and safety

Adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant

P001: Prophylaxis through Week 14 (~100 days) post-HSCT
To evaluate letermovir prophylaxis as a preventive strategy for CMV infection or disease, the efficacy of letermovir was assessed in a multicentre, 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-HSCT) and continued through Week 14 post-HSCT. Letermovir was administered either orally or intravenously; the dose of letermovir was the same regardless of the route of administration. Subjects were monitored through Week 24 post-HSCT for the primary efficacy endpoint with continued follow-up through Week 48 post-HSCT.

Subjects received CMV DNA monitoring weekly until post-HSCT week 14 and then every two weeks until post-HSCT 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-HSCT.

Among the 565 treated subjects, 373 subjects received letermovir (including 99 subjects who received at least one intravenous dose) and 192 received placebo (including 48 subjects who received at least one intravenous 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 leukaemia (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 Leucocyte 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-HSCT or had a missing outcome at Week 24 post-HSCT were counted as failures.

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

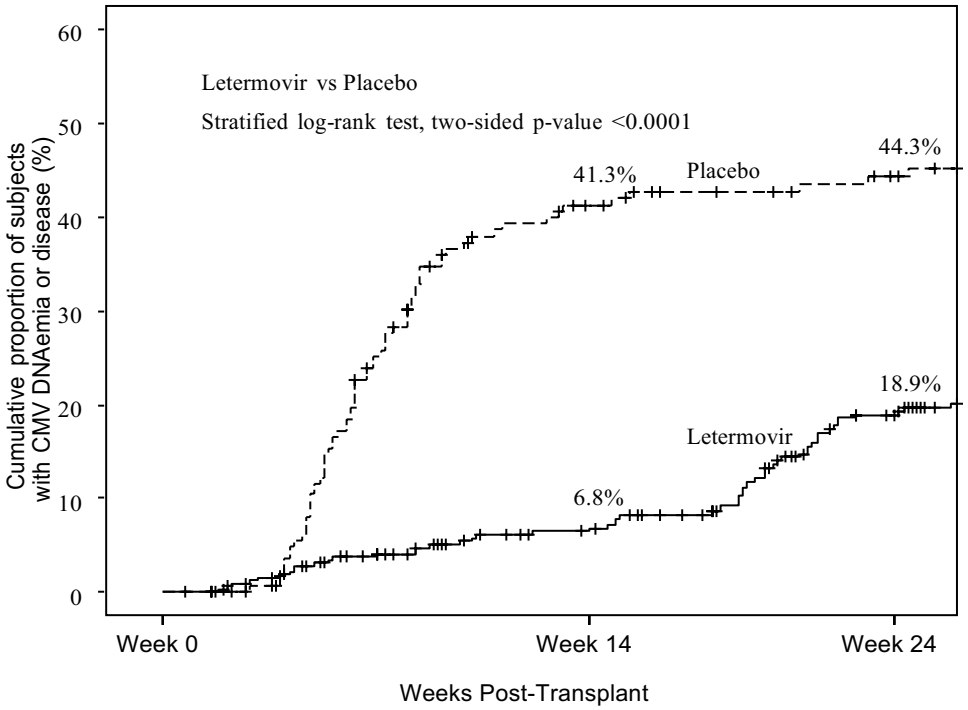
Table 4: P001: Efficacy results in HSCT recipients (NC=F Approach, FAS Population)

Parameter	**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-HSCT 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-HSCT. The estimated difference (95% CI for the difference) was -26.1% (-45.9%, -6.3%), with a nominal one-sided p-value < 0.0048.

Factors associated with CMV DNAemia after Week 14 post-HSCT 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)

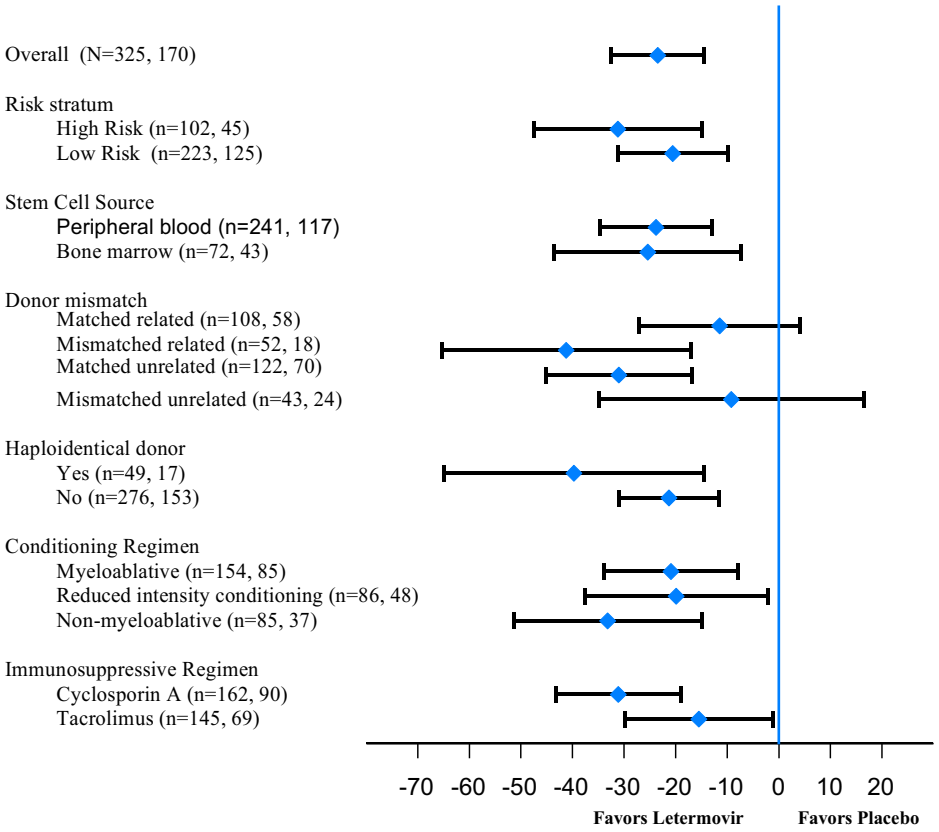


Number of Subjects at Risk			
Letermovir	325	270	212
Placebo	170	85	70

There were no differences in the incidence of or time to engraftment between the letermovir 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-HSCT 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.

P040: Prophylaxis from Week 14 (~100 days) through Week 28 (~200 days) post-HSCT
The efficacy of extending letermovir prophylaxis from Week 14 (~100 days) through Week 28 (~200 days) post-HSCT in patients at risk for late CMV infection and disease was assessed in a multicentre, double-blind, placebo-controlled Phase 3 trial (P040) in adult CMV-seropositive recipients [R+] of an allogeneic HSCT. Eligible subjects who completed letermovir prophylaxis through ~100 days post-HSCT were randomised (2:1) to receive letermovir or placebo from Week 14 through Week 28 post-HSCT. Subjects were monitored through Week 28 post-HSCT for the primary efficacy endpoint with continued off-treatment follow-up through Week 48 post-HSCT.

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

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

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

Letermovir demonstrated superior efficacy over placebo in the analysis of the primary endpoint, as shown in Table 5. The estimated treatment difference of -16.1% was statistically significant (one-sided p-value=0.0005). Efficacy consistently favored letermovir across subgroups based on subject characteristics (age, gender, race) and risk factors for late CMV infection and disease.

Table 5: P040: Efficacy results in HSCT recipients at risk for late CMV infection and disease (OF approach, FAS population)

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

* The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.
† Clinically significant CMV infection was defined as CMV end-organ disease (proven or probable) or initiation of PET based on documented CMV viremia and the clinical condition of the subject.
‡ 95% CIs and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (haploidentical donor yes or no). A one-sided p-value ≤0.0249 was used for declaring statistical significance.
Approach to handling missing values: Observed Failure (OF) approach. With the OF approach, failure was defined as all subjects who developed clinically significant CMV infection or discontinued prematurely from the study with CMV viremia from Week 14 (~100 days) through Week 28 (~200 days) post-HSCT.
N=Number of subjects in each treatment group.
n (%)=Number (percent) of subjects in each sub-category.

P002: *Adult CMV-seronegative recipients of a kidney transplant from a CMV-seropositive donor [D+/R-]*
To evaluate letermovir prophylaxis as a preventive strategy for CMV disease in kidney transplant recipients, the efficacy of letermovir was assessed in a multicentre, double-blind, active comparator-controlled non-inferiority Phase 3 trial (P002) in adult kidney transplant recipients at high risk [D+/R-]. Subjects were randomised (1:1) to receive either letermovir or valganciclovir. Letermovir was given concomitantly with acyclovir. Valganciclovir was given concomitantly with a placebo to acyclovir. Randomisation was stratified by the use or non-use of highly cytolytic, anti-lymphocyte immunotherapy during induction. Letermovir or valganciclovir were initiated between Day 0 and Day

7 post-kidney transplant and continued through Week 28 (~200 days) post-transplant. Subjects were monitored through Week 52 post-transplant.

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

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

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

Table 6: P002: Efficacy results in kidney transplant recipients (OF approach, FAS population)

Parameter	Letermovir (N=289) n (%)	Valganciclovir (N=297) n (%)
CMV disease* through Week 52	**30 (10.4)**	**35 (11.8)**
Stratum-adjusted treatment difference (Letermovir-Valganciclovir)† Difference (95% CI)	-1.4 (-6.5, 3.8)‡	

* CMV disease cases confirmed by an independent adjudication committee.
† The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (use/non-use of highly cytolytic, anti-lymphocyte immunotherapy during induction).
‡ Based on a non-inferiority margin of 10%, letermovir is non-inferior to valganciclovir.
Approach to handling missing values: Observed Failure (OF) approach. With OF approach, participants who discontinue prematurely from the study for any reason are not considered failures.
Note: Subjects randomised to the letermovir group were given acyclovir for herpes simplex virus (HSV) and varicella zoster virus (VZV) prophylaxis. Subjects randomised to the valganciclovir group were given a placebo to acyclovir.
N=number of subjects in each treatment group.
n (%)=Number (percent) of subjects in each sub-category.

Efficacy was comparable across all subgroups, including sex, age, race, region, and the use/non-use of highly cytolytic, anti-lymphocyte immunotherapy during induction.

Paediatric population

P030: *Paediatric recipients of an allogeneic hematopoietic stem cell transplant*
To evaluate letermovir prophylaxis as a preventive strategy for CMV infection or disease in paediatric transplant recipients, the efficacy of letermovir was assessed in a multicentre, open-label, single-arm Phase 2b trial (P030) in paediatric recipients of an allogeneic HSCT. Study drug was initiated after HSCT (Day 0-28 post-HSCT) and continued through Week 14 post-HSCT. Study drug was administered either orally or intravenously; the dose of letermovir was based on age, body weight and formulation.

Among the 63 treated subjects, 8 were 0 to less than 2 years of age, 27 were 2 to less than 12 years of age and 28 were 12 to less than 18 years of age. At baseline, 87% of subjects received a myeloablative regimen, 67% were receiving cyclosporine, and 27% were receiving tacrolimus. The most common primary reasons for transplant were acute myeloid leukaemia (18%) and aplastic anaemia (10%) in the

overall population, and combined immunodeficiency (37.5%) and familial haemophagocytic lymphohistiocytosis (25.0%) in children less than 2 years of age.

Secondary efficacy endpoint
The efficacy endpoints of P030 were secondary and included the incidence of clinically significant CMV infection through Week 14 post-HSCT and through Week 24 post-HSCT. Clinically significant CMV infection was defined as the occurrence of either CMV end-organ disease, or initiation of anti-CMV PET based on documented CMV viremia and the clinical condition of the subject. The incidence of clinically significant CMV infection was 7.1% and 10.7% through Week 14 post-HSCT and Week 24 post-HSCT, respectively.

5.2 Pharmacokinetic properties

In healthy adult subjects, the pharmacokinetics of letermovir have been characterised following oral and intravenous administration. Letermovir exposure increased in a greater than dose-proportional manner with both oral or intravenous administration. The mechanism is likely saturation/autoinhibition of OATP1B1/3. The pharmacokinetics of letermovir have also been characterised following oral and intravenous administration in adult HSCT recipients (see Table 7) and paediatric HSCT recipients (see Table 9 and Table 10) and following oral administration in adult kidney transplant recipients (see Table 8).

Healthy adult 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}.

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

Table 7: Letermovir AUC (ng•hr/mL) values in adult HSCT Recipients

Treatment Regimen	Median (90% Prediction Interval)*
480 mg Oral, no cyclosporine	34 400 (16 900, 73 700)
480 mg intravenous, no cyclosporine	100 000 (65 300, 148 000)
240 mg Oral, with cyclosporine	60 800 (28 700, 122 000)
240 mg intravenous, with cyclosporine	70 300 (46 200, 106 000)
* Population post-hoc predictions from the population PK analysis using Phase 3 data	

Adult kidney transplant recipients
Letermovir AUC was estimated using population pharmacokinetic analysis using P002 Phase 3 data (see Table 8). Efficacy was consistent across the range of exposures observed in P002.

Table 8: Letermovir AUC (ng•hr/mL) values in adult kidney transplant recipients

Treatment Regimen	Median (90% Prediction Interval)*
480 mg Oral, no cyclosporine	62 200 (28 900, 145 000)
240 mg Oral, with cyclosporine	57 700 (26 900, 135 000)
* Medians and 90% prediction intervals are based on simulations using the Phase 3 population PK model with inter-individual variability. Note: PK of letermovir was not studied following intravenous administration in kidney transplant recipients; however, the projected AUC following intravenous administration is similar to the model predicted AUC following intravenous administration in HSCT recipients (see Table 7).	

Absorption

In healthy adult subjects, 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 adult 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%. In adult kidney transplant recipients, bioavailability of letermovir was estimated to be approximately 60% with 480 mg once daily oral letermovir administered without cyclosporine.

Effect of cyclosporine
In adult 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 in adult and paediatric patients weighing at least 30 kg (see section 4.2). If intravenous letermovir is co-administered with cyclosporine in paediatric patients weighing less than 30 kg, dose adjustment is not required (see section 4.2).

Effect of food
In healthy adult subjects, oral administration of 480 mg single dose of letermovir tablet 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 tablets may be administered orally with or without food as has been done in the clinical trials (see section 4.2).

In healthy adult subjects, oral administration of 240 mg single dose of letermovir granules with soft foods (pudding or applesauce) resulted in an approximately 13% and 20% increase in overall exposure (AUC) and resulted in approximately 25% and 33% increase in peak levels (C_{max}) of letermovir. Letermovir granules may be administered with soft foods, as has been done in the paediatric trial (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 adult 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 intravenous letermovir in healthy adult 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 adult 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 adult 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 adult subjects. The changes in letermovir exposure in adult 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
Clinical study in a renally impaired population
Letermovir unbound AUC was approximately 115- and 81% higher in adult 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 adult 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.

Post-kidney transplant (P002)
Based on population pharmacokinetic analysis, letermovir AUC was approximately 12%, 27% and 35% higher in adult subjects with mild (CrCl greater than or equal to 60 to less than 90 mL/min), moderate (CrCl greater than or equal to 30 to less than 60 mL/min) and severe (CrCl greater than or equal to 15 to less than 30 mL/min) renal impairment, respectively, compared to adult subjects with CrCl greater than or equal to 90 mL/min. These changes are not considered to be clinically relevant.

Weight
Based on population pharmacokinetic analyses in healthy adult subjects, letermovir AUC is estimated to be 18.7% lower in subjects weighing 80-100 kg compared to subjects weighing 67 kg. Based on population pharmacokinetic analysis in adult kidney transplant recipients (P002), letermovir AUC is estimated to be 26% lower in subjects weighing greater than 80 kg compared to subjects weighing less than or equal to 80 kg. These differences are not clinically relevant.

Race
Based on population pharmacokinetic analyses in healthy adult subjects, 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 adult 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.

Paediatric population
Letermovir AUC in paediatric HSCT recipients was estimated via population pharmacokinetic analysis using observed PK data from study P030 (see Table 9 and Table 10). Exposures for paediatric HSCT recipients across body weight bands are within the range of exposures achieved in the adult HSCT reference exposures (see Table 7).

Table 9: Letermovir AUC (ng•hr/mL) values following oral administration in paediatric HSCT recipients

Body weight	Oral dose, no cyclosporine	Median (90% prediction interval)*	Oral dose, with cyclosporine	Median (90% prediction interval)*
30 kg and above	480 mg	39 100 (18 700-81 300)	240 mg	49 100 (23 200-104 000)
15 kg to less than 30 kg	240 mg	38 900 (20 200-74 300)	120 mg	51 000 (26 600-98 200)
7.5 kg to less than 15 kg	120 mg	32 000 (16 700-59 300)	60 mg	41 600 (22 300-81 100)
5 kg to less than 7.5 kg	80 mg	30 600 (16 200-55 000)	40 mg	39 000 (20 600-72 000)
* Medians and 90% prediction intervals are based on simulations using the paediatric HSCT population PK model with inter-individual variability.				

Table 10: Letermovir AUC (ng•hr/mL) values following intravenous administration in paediatric HSCT recipients

Body weight	Intravenous dose, no cyclosporine	Median (90% prediction interval)*	Intravenous dose, with cyclosporine	Median (90% prediction interval)*
30 kg and above	480 mg	111 000 (55 700-218 000)	240 mg	59 800 (28 400-120 000)
15 kg to less than 30 kg	120 mg	57 200 (29 700-113 000)	120 mg	61 100 (29 900-121 000)
7.5 kg to less than 15 kg	60 mg	46 000 (24 300-83 900)	60 mg	49 200 (25 800-93 800)
5 kg to less than 7.5 kg	40 mg	43 400 (24 300-81 000)	40 mg	45 900 (24 900-82 200)
* Medians and 90% prediction intervals are based on simulations using the paediatric HSCT population PK model with inter-individual variability.				

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 characterised 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 intravenous letermovir formulated with 1 500 mg/kg/day of the cyclodextrin excipient hydroxypropylbetadex.

Parenteral administration of hydroxypropylbetadex at ≥ 2 000 mg/kg has been associated with hearing loss resulting from damage to the inner ear in multiple animal species. By comparison, the maximum dose of hydroxypropylbetadex (120 mg/kg) in intravenous PREVYMIS at the maximum recommended human dose (MRHD) (120 mg/kg) has not been associated with hearing loss in any animal studies. The active ingredient, letermovir, is not known to be associated with ototoxicity.

Carcinogenesis

A 6-month oral carcinogenicity study in RasH2 transgenic (Tg.RasH2) mice showed no evidence of human-relevant tumorigenesis up to the highest doses tested, 150 mg/kg/day and 300 mg/kg/day in males and females, respectively.

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 sulphate, 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 intravenous 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: 3 years
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
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 intravenous 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.

For the **480 mg or 240 mg dose**, 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 intravenous bag containing either sodium chloride 9 mg/mL (0.9%) solution for injection or 5% dextrose, and mix the diluted solution by gentle inversion. Do not shake. If a vial is added to a 250 mL intravenous 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).

For the **120 mg or 60 mg dose**, prepare PREVYMIS concentrate for solution for infusion according to Table 11 below in sodium chloride 9 mg/mL (0.9%) solution for injection or 5% dextrose, and mix the diluted solution by gentle inversion. Do not shake.

For the **40 mg dose**, prepare PREVYMIS concentrate for solution for infusion according to Table 12 below in either sodium chloride 9 mg/mL (0.9%) solution for injection or 5% dextrose, and mix the diluted solution by gentle inversion. Do not shake.

Table 11: Preparation of PREVYMIS intravenous solution for doses of 120 mg or 60 mg

Intravenous dose	Volume of 20 mg/mL PREVYMIS concentrate for solution for infusion	Final infusion volume	Final concentration of letermovir
120 mg	6 mL of 20 mg/mL	75 mL	1.6 mg/mL
60 mg	3 mL of 20 mg/mL	50 mL	1.2 mg/mL

Table 12: Preparation of PREVYMIS intravenous solution for a dose of 40 mg

Intravenous dose	Volume of 2 mg/mL PREVYMIS dilution (1:10)*	Final infusion volume	Final concentration of letermovir
40 mg	20 mL of 2 mg/mL	20 mL	2 mg/mL
* To prepare 2 mg/mL PREVYMIS dilution, add 5 mL of 20 mg/mL PREVYMIS concentrate for solution for infusion from the vial to 45 mL of diluent (sodium chloride 9 mg/mL (0.9%) solution for injection or 5% dextrose) and mix gently.			

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.

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
Date of latest renewal: 24 August 2022

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

PREVYMIS 20 mg granules in sachet
PREVYMIS 120 mg granules in sachet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PREVYMIS 20 mg granules in sachet

Each sachet contains 20 mg of letermovir.

PREVYMIS 120 mg granules in sachet

Each sachet contains 120 mg of letermovir.

Excipients with known effect

Each 20 mg granules in sachet contains 1.7 mg of lactose (as monohydrate).
Each 120 mg granules in sachet contains 9.9 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules in sachet (granules)

Beige granules approximately 2 mm in diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PREVYMIS is indicated for prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult and paediatric patients weighing at least 5 kg who are CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT).

PREVYMIS is indicated for prophylaxis of CMV disease in CMV-seronegative adult and paediatric patients weighing at least 40 kg who have received a kidney transplant from a CMV-seropositive donor [D+/R-].

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

4.2 Posology and method of administration

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

Posology

Letermovir is also available as film-coated tablets (240 mg and 480 mg) and as concentrate for solution for infusion (240 mg and 480 mg).

Letermovir tablets, granules in sachet, and concentrate for solution for infusion may be used interchangeably at the discretion of the physician. Dose adjustment may be necessary for paediatric

patients weighing less than 30 kg when switching between oral and intravenous formulations. Refer to the prescribing information for the letermovir concentrate for solution for infusion for dosing information.

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

Prolonged letermovir prophylaxis beyond 100 days post-HSCT may be of benefit in some patients at high risk for late CMV reactivation (see section 5.1). The safety and efficacy of letermovir use for more than 200 days has not been studied in clinical trials.

Adult and paediatric patients weighing at least 30 kg who are HSCT recipients
The recommended dose of letermovir is 480 mg once daily that can be administered as four 120 mg sachets.

Dose adjustment in adult and paediatric patients weighing at least 30 kg who are HSCT recipients
If letermovir is co-administered with cyclosporine, the dose of letermovir should be decreased to 240 mg once daily (see sections 4.5 and 5.2).

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

Paediatric patients weighing less than 30 kg who are HSCT recipients
The recommended doses of letermovir for paediatric patients weighing less than 30 kg are shown in Table 1 (see also section 5.2). Letermovir should be administered once daily.

Letermovir film-coated tablets can be used for patients who can swallow tablets. Refer to the prescribing information for letermovir film-coated tablet dosing information.

Dose adjustment in paediatric patients weighing less than 30 kg who are HSCT recipients
If oral letermovir is co-administered with cyclosporine, the dose of letermovir should be decreased as shown in Table 1 (see also sections 4.5 and 5.2).

- If cyclosporine is initiated after starting letermovir, the next dose of letermovir should be the daily oral dose co-administered with cyclosporine (see Table 1).
- If cyclosporine is discontinued after starting letermovir, the next dose of letermovir should be the daily oral dose administered without cyclosporine (see Table 1).
- If cyclosporine dosing is temporarily interrupted due to high cyclosporine levels, no dose adjustment of letermovir is needed.

Table 1: Recommended dose of letermovir granules in sachet without or with cyclosporine in paediatric patients weighing less than 30 kg

Body weight	Administered without cyclosporine		Co-administered with cyclosporine	
	Daily oral dose	Number of letermovir sachets once daily	Daily oral dose	Number of letermovir sachets once daily
15 kg to less than 30 kg	240 mg	Two 120 mg sachets	120 mg	One 120 mg sachet
7.5 kg to less than 15 kg	120 mg	One 120 mg sachet	60 mg	Three 20 mg sachets
5 kg to less than 7.5 kg	80 mg	Four 20 mg sachets	40 mg	Two 20 mg sachets

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

Adult and paediatric patients weighing at least 40 kg who are kidney transplant recipients
The recommended dose of letermovir is 480 mg once daily that can be administered as four 120 mg sachets.

Dose adjustment in adult and paediatric patients weighing at least 40 kg who are kidney transplant recipients
If letermovir is co-administered with cyclosporine, the dose of letermovir should be decreased to 240 mg once daily (see sections 4.5 and 5.2).

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

Missed dose
Patients should be instructed that if they miss a dose of letermovir, they should take it as soon as they remember. If they do not remember until it is time for the next dose, they should skip the missed dose and go back to the regular schedule. Patients should not double their next dose or take more than the prescribed dose.

Special populations

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

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

Combined hepatic and renal impairment
Letermovir 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 letermovir 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.

Paediatric population
The safety and efficacy of letermovir in HSCT patients weighing less than 5 kg or in kidney transplant patients weighing less than 40 kg have not been established. No data are available. No recommendation on posology for kidney transplant patients weighing less than 40 kg could be supported by pharmacokinetic/pharmacodynamic extrapolation.

Method of administration
For oral use (by ingestion or via an enteral feeding tube).

Administer letermovir granules orally mixed with 1 to 3 teaspoons of soft food or via nasogastric tube (NG tube) or gastric tube (G tube) (see section 6.6). Do not crush or chew because these methods have not been studied. Additional food or a meal can be consumed following administration.

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 in HSCT recipients

In a Phase 3 trial (P001), the safety and efficacy of letermovir has been established in HSCT 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 every two weeks 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 letermovir 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 2 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

Letermovir 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 2).

Excipients

PREVYMIS contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per sachet, that is to say essentially 'sodium-free'.

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 2).

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 metabolising enzymes or transporters

Co-administration of letermovir (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 2).
-Examples of strong inducers include rifampicin, phenytoin, carbamazepine, 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 2).

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

Inhibitors of OATP1B1 or 3
Co-administration of letermovir with medicinal products that are inhibitors of OATP1B1/3 transporters may result in increased letermovir plasma concentrations. If letermovir is co-administered with cyclosporine (a potent OATP1B1/3 inhibitor), the recommended dose of letermovir is 240 mg once daily in adult and paediatric patients weighing at least 30 kg (see Table 2 and sections 4.2 and 5.2). If oral letermovir is co-administered with cyclosporine in paediatric patients weighing less than 30 kg, the dose should be decreased (see 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 letermovir with oral midazolam (a CYP3A substrate) results in 2-3-fold increased midazolam plasma concentrations. Co-administration of letermovir 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 2). 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 letermovir 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 2). Comparing letermovir regimen administered without cyclosporine, the effect is more marked after intravenous than oral letermovir.
The magnitude of the OATP1B1/3 inhibition on co-administered medicinal products is likely greater when letermovir 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 letermovir 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 2).
The effect is expected to be less pronounced for oral letermovir without cyclosporine, than intravenous 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 2). 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 letermovir 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 a 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.

General information

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

Table 2 provides a listing of established or potentially clinically significant medicinal product interactions. The medicinal product interactions described are based on adult studies conducted with letermovir or are predicted medicinal product interactions that may occur with letermovir (see sections 4.3, 4.4, 5.1, and 5.2).

Table 2: 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 in adults 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 intravenously, 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 letermovir**
Antibiotics		
nafcillin	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	Nafcillin may decrease plasma concentrations of letermovir. Co-administration of letermovir and nafcillin is not recommended.
Antifungals		
fluconazole (400 mg single dose)/letermovir (480 mg single dose)	↔ fluconazole AUC 1.03 (0.99, 1.08) C_{max} 0.95 (0.92, 0.99) ↔ letermovir AUC 1.11 (1.01, 1.23) C_{max} 1.06 (0.93, 1.21) Interaction at steady state not studied. Expected: ↔ fluconazole ↔ letermovir	No dose adjustment required.
itraconazole (200 mg once daily PO)/letermovir (480 mg once daily PO)	↔ itraconazole AUC 0.76 (0.71, 0.81) C_{max} 0.84 (0.76, 0.92) ↔ letermovir AUC 1.33 (1.17, 1.51) C_{max} 1.21 (1.05, 1.39)	No dose adjustment required.
posaconazole[‡] (300 mg single dose)/ letermovir (480 mg daily)	↔ posaconazole AUC 0.98 (0.82, 1.17) C_{max} 1.11 (0.95, 1.29)	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 letermovir
voriconazole‡ (200 mg twice daily)/ letermovir (480 mg daily)	↓ voriconazole AUC 0.56 (0.51, 0.62) C_{max} 0.61 (0.53, 0.71) (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.
Antimycobacterials		
rifabutin	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	Rifabutin may decrease plasma concentrations of letermovir. Co-administration of letermovir and rifabutin is not recommended.
rifampicin		Multiple dose rifampicin decreases plasma concentrations of letermovir. Co-administration of letermovir and rifampicin is not recommended.
(600 mg single dose PO)/ letermovir (480 mg single dose PO)	↔letermovir AUC 2.03 (1.84, 2.26) C_{max} 1.59 (1.46, 1.74) C_{24} 2.01 (1.59, 2.54) (OATP1B1/3 and/or P-gp inhibition)	
(600 mg single dose intravenous)/ letermovir (480 mg single dose PO)	↔ letermovir AUC 1.58 (1.38, 1.81) C_{max} 1.37 (1.16, 1.61) C_{24} 0.78 (0.65, 0.93) (OATP1B1/3 and/or P-gp inhibition)	
(600 mg once daily PO)/ letermovir (480 mg once daily PO)	↓ letermovir AUC 0.81 (0.67, 0.98) C_{max} 1.01 (0.79, 1.28) C_{24} 0.14 (0.11, 0.19) (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 AUC 0.15 (0.13, 0.17) C_{max} 0.27 (0.22, 0.31) C_{24} 0.09 (0.06, 0.12) (P-gp/UGT induction)	
Antipsychotics		
thioridazine	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	Thioridazine may decrease plasma concentrations of letermovir. Co-administration of letermovir and thioridazine is not recommended.
Endothelin antagonists		
bosentan	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	Bosentan may decrease plasma concentrations of letermovir. Co-administration of letermovir and bosentan is not recommended.

Concomitant medicinal product	Effect on concentration† mean ratio (90% confidence interval) for AUC, C_{max} (likely mechanism of action)	Recommendations concerning co-administration with letermovir
Antivirals		
acyclovir‡ (400 mg single dose)/ letermovir (480 mg daily)	↔ acyclovir AUC 1.02 (0.87, 1.2) C_{max} 0.82 (0.71, 0.93)	No dose adjustment required.
valacyclovir	Interaction not studied. Expected: ↔ valacyclovir	No dose adjustment required.
Herbal products		
St. John's wort (*Hypericum perforatum*)	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	St. John's wort may decrease plasma concentrations of letermovir. Co-administration of letermovir and St. John's wort is contraindicated.
HIV medicinal products		
efavirenz	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction) ↑ or ↓ efavirenz (CYP2B6 inhibition or induction)	Efavirenz may decrease plasma concentrations of letermovir. Co-administration of letermovir and efavirenz is not recommended.
etravirine, nevirapine, ritonavir, lopinavir	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	These antivirals may decrease plasma concentrations of letermovir. Co-administration of letermovir with these antivirals is not recommended.
HMG-CoA reductase inhibitors		
atorvastatin‡ (20 mg single dose)/ letermovir (480 mg daily)	↑ atorvastatin AUC 3.29 (2.84, 3.82) C_{max} 2.17 (1.76, 2.67) (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 letermovir#. Although not studied, when letermovir is co-administered with cyclosporine, the magnitude of the increase in atorvastatin plasma concentrations is expected to be greater than with letermovir alone. When letermovir is co-administered with cyclosporine, atorvastatin is contraindicated.
simvastatin, pitavastatin, rosuvastatin	Interaction not studied. Expected: ↑ HMG-CoA reductase inhibitors (CYP3A, OATP1B1/3 inhibition)	Letermovir may substantially increase plasma concentrations of these statins. Concomitant use is not recommended with letermovir alone. When letermovir 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 letermovir**
fluvastatin, pravastatin	Interaction not studied. Expected: ↑ HMG-CoA reductase inhibitors (OATP1B1/3 and/or BCRP inhibition)	Letermovir may increase statin plasma concentrations. When letermovir is co-administered with these statins, a statin dose reduction may be necessary[#]. Statin-associated adverse events such as myopathy should be closely monitored. When letermovir 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 AUC 1.66 (1.51, 1.82) C_{max} 1.08 (0.97, 1.19) (CYP3A inhibition)	If letermovir is co-administered with cyclosporine, the dose of letermovir should be decreased to 240 mg once daily in adults (see sections 4.2 and 5.1) and paediatric patients weighing at least 30 kg (see section 4.2). If oral letermovir is co-administered with cyclosporine in paediatric patients weighing less than 30 kg, the dose should be decreased (see section 4.2). Frequent monitoring of cyclosporine whole blood concentrations should be performed during treatment, when changing letermovir administration route, and at discontinuation of letermovir and the dose of cyclosporine adjusted accordingly[#].
cyclosporine (200 mg single dose)/ letermovir (240 mg daily)	↑ letermovir AUC 2.11 (1.97, 2.26) C_{max} 1.48 (1.33, 1.65) (OATP1B1/3 inhibition)	
mycophenolate mofetil (1 g single dose)/ letermovir (480 mg daily)	↔mycophenolic acid AUC 1.08 (0.97, 1.20) C_{max} 0.96 (0.82, 1.12) ↔ letermovir AUC 1.18 (1.04, 1.32) 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 letermovir**
sirolimus[‡] (2 mg single dose)/ letermovir (480 mg daily)	↑ sirolimus AUC 3.40 (3.01, 3.85) C_{max} 2.76 (2.48, 3.06) (CYP3A inhibition) Interaction not studied. Expected: ↔ letermovir	Frequent monitoring of sirolimus whole blood concentrations should be performed during treatment, when changing letermovir administration route, and at discontinuation of letermovir and the dose of sirolimus adjusted accordingly[#]. Frequent monitoring of sirolimus concentrations is recommended at initiation or discontinuation of cyclosporine co-administration with letermovir. When letermovir is co-administered with cyclosporine, also refer to the sirolimus prescribing information for specific dosing recommendations for use of sirolimus with cyclosporine. When letermovir is co-administered with cyclosporine, the magnitude of the increase in concentrations of sirolimus may be greater than with letermovir alone.
tacrolimus (5 mg single dose)/ letermovir (480 mg daily)	↑ tacrolimus AUC 2.42 (2.04, 2.88) C_{max} 1.57 (1.32, 1.86) (CYP3A inhibition)	Frequent monitoring of tacrolimus whole blood concentrations should be performed during treatment, when changing letermovir administration route, and at discontinuation of letermovir and the dose of tacrolimus adjusted accordingly[#].
tacrolimus (5 mg single dose)/ letermovir (80 mg twice daily)	↔ letermovir AUC 1.02 (0.97, 1.07) 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 AUC 1.42 (1.32, 1.52) C_{max} 0.89 (0.83, 0.96) ↔ LNG AUC 1.36 (1.30, 1.43) 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. 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 letermovir
Antidiabetic medicinal products		
repaglinide	Interaction not studied. Expected: ↑ or ↓ repaglinide (CYP2C8 induction, CYP2C8 and OATP1B inhibition)	Letermovir may increase or decrease the plasma concentrations of repaglinide. (The net effect is not known). Concomitant use is not recommended. When letermovir 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. Expected: ↑ glyburide (OATP1B1/3 inhibition CYP3A inhibition, CYP2C9 induction)	Letermovir may increase the plasma concentrations of glyburide. 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. When letermovir is co-administered with cyclosporine, refer also to the glyburide prescribing information for specific dosing recommendations.
Antiepileptic medicinal products (see also general text)		
carbamazepine, phenobarbital	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	Carbamazepine or phenobarbital may decrease plasma concentrations of letermovir. Co-administration of letermovir and carbamazepine or phenobarbital is not recommended.
phenytoin	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction) ↓ phenytoin (CYP2C9/19 induction)	Phenytoin may decrease plasma concentrations of letermovir. Letermovir may decrease the plasma concentrations of phenytoin. Co-administration of letermovir and phenytoin is not recommended.

Concomitant medicinal product	Effect on concentration† mean ratio (90% confidence interval) for AUC, C_{max} (likely mechanism of action)	Recommendations concerning co-administration with letermovir
Oral anticoagulants		
warfarin	Interaction not studied. Expected: ↓ warfarin (CYP2C9 induction)	Letermovir may decrease the plasma concentrations of warfarin. Frequent monitoring of International Normalised Ratio (INR) should be performed when warfarin is co-administered with letermovir treatment#. 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. Expected: ↓ dabigatran (intestinal P-gp induction)	Letermovir may decrease the plasma concentrations of dabigatran and may decrease efficacy of dabigatran. Concomitant use of dabigatran should be avoided due to the risk of reduced dabigatran efficacy. When letermovir is co-administered with cyclosporine, dabigatran is contraindicated.
Sedatives		
midazolam (1 mg single dose intravenous)/ letermovir (240 mg once daily PO) midazolam (2 mg single dose PO) / letermovir (240 mg once daily PO)	↑ midazolam Intravenous: AUC 1.47 (1.37, 1.58) C_{max} 1.05 (0.94, 1.17) PO : AUC 2.25 (2.04, 2.48) C_{max} 1.72 (1.55, 1.92) (CYP3A inhibition)	Close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised during co-administration of letermovir 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.

Concomitant medicinal product	Effect on concentration† mean ratio (90% confidence interval) for AUC, C_{max} (likely mechanism of action)	Recommendations concerning co-administration with letermovir
Opioid agonists		
Examples: alfentanil, fentanyl	Interaction not studied. Expected: ↑ CYP3A metabolised opioids (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 letermovir 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 letermovir 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. Expected: ↑ amiodarone (primarily CYP3A inhibition and CYP2C8 inhibition or induction)	Letermovir may increase the plasma concentrations of amiodarone. 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 letermovir#.
quinidine	Interaction not studied. Expected: ↑ quinidine (CYP3A inhibition)	Letermovir may increase the plasma concentrations of quinidine. Close clinical monitoring should be exercised during administration of letermovir with quinidine. Refer to the respective prescribing information#.
Cardiovascular medicinal products		
digoxin‡ (0.5 mg single dose)/ letermovir (240 mg twice daily)	↔ digoxin AUC 0.88 (0.80, 0.96) C_{max} 0.75 (0.63, 0.89) (P-gp induction)	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 letermovir
Proton pump inhibitors		
omeprazole	Interaction not studied. Expected: ↓omeprazole (induction of CYP2C19) Interaction not studied. Expected: ↔ letermovir	Letermovir may decrease the plasma concentrations of CYP2C19 substrates. Clinical monitoring and dose adjustment may be needed.
pantoprazole	Interaction not studied. Expected: ↓ pantoprazole (likely due to induction of CYP2C19) Interaction not studied. Expected: ↔ letermovir	Letermovir may decrease the plasma concentrations of CYP2C19 substrates. Clinical monitoring and dose adjustment may be needed.
Wakefulness-promoting agents		
modafinil	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	Modafinil may decrease plasma concentrations of letermovir. Co-administration of letermovir 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).

Letermovir 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 letermovir 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 (see section 5.3).

4.7 Effects on ability to drive and use machines

Letermovir may have minor influence on the ability to drive or use machines. Fatigue and vertigo have been reported in some patients during treatment with letermovir, 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 letermovir was based on three Phase 3 clinical trials.

HSCT
In P001, 565 adult HSCT recipients received letermovir 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 letermovir 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 letermovir were: nausea (1.6%), vomiting (0.8%), and abdominal pain (0.5%).

In P040, 218 adult HSCT recipients received letermovir or placebo from Week 14 (~100 days) through Week 28 (~200 days) post-HSCT and were followed for safety through Week 48 post-HSCT (see section 5.1). The adverse reactions reported were consistent with the safety profile of letermovir as characterised in study P001.

Kidney transplant
In P002, 292 adult kidney transplant recipients received letermovir through Week 28 (~200 days) post-transplant (see section 5.1).

Tabulated summary of adverse reactions

The following adverse reactions were identified in adult patients taking letermovir 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 3: Adverse reactions identified with letermovir

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

Paediatric population

The safety assessment of letermovir in paediatric patients from birth up to 18 years old was based on a Phase 2b clinical trial (P030). In P030, 63 HSCT recipients were treated with letermovir through Week 14 post-HSCT. Their age distribution was as follows, i.e., 28 adolescents, 14 children aged 7 to less than 12 years, 13 aged 2 to less than 7 years, and 8 less than 2 years old (5 of them less than 1 year old). The adverse reactions were consistent with those observed in clinical studies of letermovir in adults.

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 letermovir. During Phase 1 clinical trials, 86 healthy adult subjects received doses ranging from 720 mg/day to 1 440 mg/day of letermovir 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 letermovir. 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 letermovir 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 pUL51 substitution A95V or 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 trials (see below).

In clinical trials
In a Phase 2b trial evaluating letermovir doses of 60, 120, or 240 mg/day or placebo for up to 84 days in 131 adult 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 adult 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.

In a Phase 3 trial (P040), DNA sequence analysis of the entire coding regions of UL51, UL56 and UL89 was performed on samples obtained from 32 adult subjects (regardless of treatment group) who experienced prophylaxis failure or who discontinued early with CMV viremia. There were no letermovir resistance-associated substitutions detected above the validated assay limit of 5%.

In a Phase 3 trial (P002), DNA sequence analysis of the entire coding regions of UL51, UL56 and UL89 was performed on samples obtained from 52 letermovir-treated adult subjects who experienced CMV disease or who discontinued early with CMV viremia. There were no letermovir resistance-associated substitutions detected above the validated assay limit of 5%.

In a Phase 2b trial (P030), DNA sequence analysis of the entire coding regions of UL51, UL56 and UL89 was performed on samples obtained from 10 letermovir-treated paediatric subjects at a visit for evaluation of CMV infection. A total of 2 letermovir resistance-associated substitutions both mapping to pUL56 were detected in 2 subjects. One subject had the substitution R369S and the other subject had the substitution C325W.

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 intravenously 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 adult subjects. Letermovir does not prolong QTc to any clinically relevant extent following the 960 mg intravenous dose with plasma concentrations approximately 2-fold higher than the 480 mg intravenous dose.

Clinical efficacy and safety

Adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant

P001: Prophylaxis through Week 14 (~100 days) post-HSCT
To evaluate letermovir prophylaxis as a preventive strategy for CMV infection or disease, the efficacy of letermovir was assessed in a multicentre, 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-HSCT) and continued through Week 14 post-HSCT. Letermovir was administered either orally or intravenously; the dose of letermovir was the same regardless of the route of administration. Subjects were monitored through Week 24 post-HSCT for the primary efficacy endpoint with continued follow-up through Week 48 post-HSCT.

Subjects received CMV DNA monitoring weekly until post-HSCT week 14 and then every two weeks until post-HSCT 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-HSCT.

Among the 565 treated subjects, 373 subjects received letermovir (including 99 subjects who received at least one intravenous dose) and 192 received placebo (including 48 subjects who received at least one intravenous 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 leukaemia (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 Leucocyte 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-HSCT or had a missing outcome at Week 24 post-HSCT were counted as failures.

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

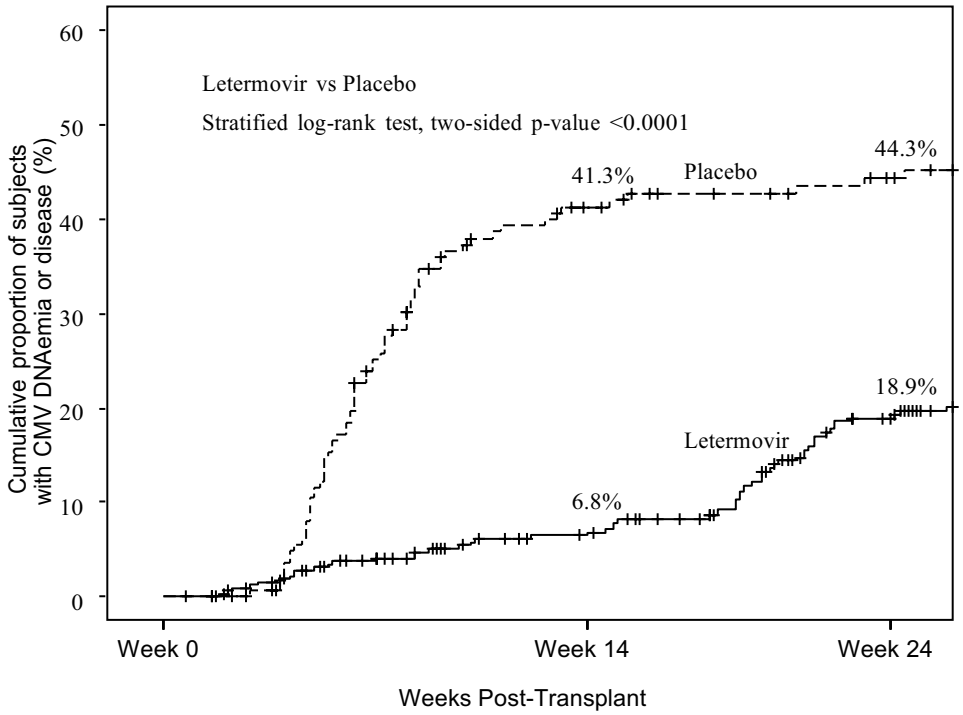
Table 4: P001: Efficacy results in HSCT recipients (NC=F Approach, FAS Population)

Parameter	**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-HSCT 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-HSCT. The estimated difference (95% CI for the difference) was -26.1% (-45.9%, -6.3%), with a nominal one-sided p-value < 0.0048.

Factors associated with CMV DNAemia after Week 14 post-HSCT 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)

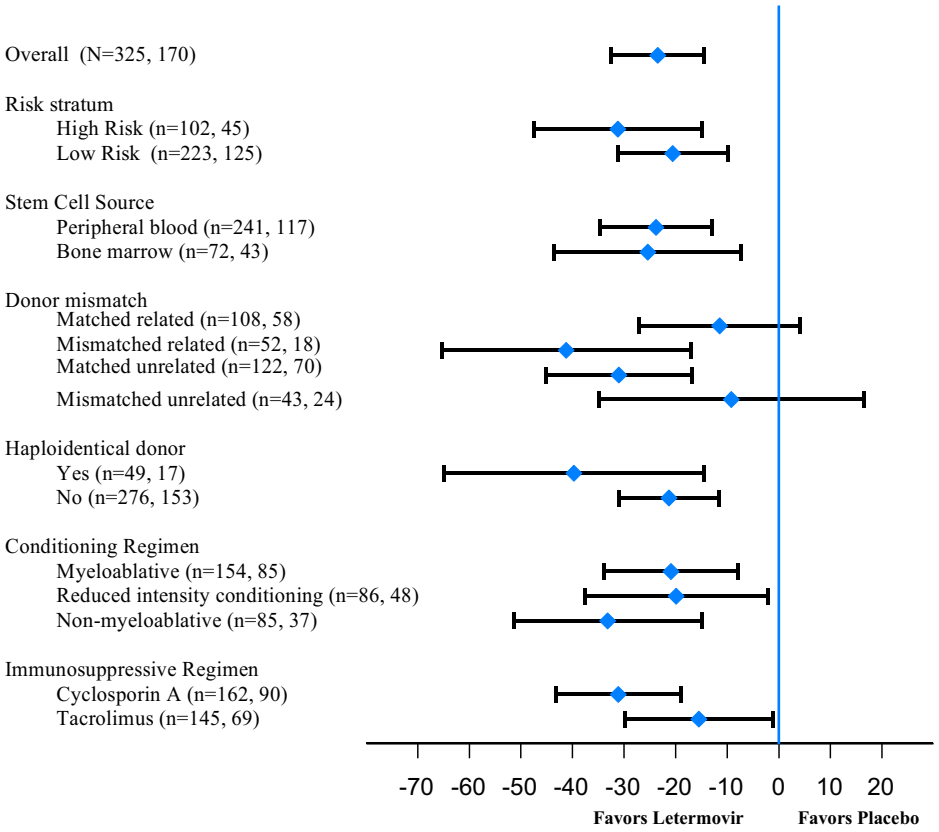


Number of Subjects at Risk			
Letermovir	325	270	212
Placebo	170	85	70

There were no differences in the incidence of or time to engraftment between the letermovir 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-HSCT 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.

P040: Prophylaxis from Week 14 (~100 days) through Week 28 (~200 days) post-HSCT
The efficacy of extending letermovir prophylaxis from Week 14 (~100 days) through Week 28 (~200 days) post-HSCT in patients at risk for late CMV infection and disease was assessed in a multicentre, double-blind, placebo-controlled Phase 3 trial (P040) in adult CMV-seropositive recipients [R+] of an allogeneic HSCT. Eligible subjects who completed letermovir prophylaxis through ~100 days post-HSCT were randomised (2:1) to receive letermovir or placebo from Week 14 through Week 28 post-HSCT. Subjects were monitored through Week 28 post-HSCT for the primary efficacy endpoint with continued off-treatment follow-up through Week 48 post-HSCT.

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

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

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

Letermovir demonstrated superior efficacy over placebo in the analysis of the primary endpoint, as shown in Table 5. The estimated treatment difference of -16.1% was statistically significant (one-sided p-value=0.0005). Efficacy consistently favored letermovir across subgroups based on subject characteristics (age, gender, race) and risk factors for late CMV infection and disease.

Table 5: P040: Efficacy results in HSCT recipients at risk for late CMV infection and disease (OF approach, FAS population)

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

* The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.
† Clinically significant CMV infection was defined as CMV end-organ disease (proven or probable) or initiation of PET based on documented CMV viremia and the clinical condition of the subject.
‡ 95% CIs and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (haploidentical donor yes or no). A one-sided p-value ≤0.0249 was used for declaring statistical significance.
Approach to handling missing values: Observed Failure (OF) approach. With the OF approach, failure was defined as all subjects who developed clinically significant CMV infection or discontinued prematurely from the study with CMV viremia from Week 14 (~100 days) through Week 28 (~200 days) post-HSCT.
N=Number of subjects in each treatment group.
n (%)=Number (percent) of subjects in each sub-category.

P002: *Adult CMV-seronegative recipients of a kidney transplant from a CMV-seropositive donor [D+/R-]*
To evaluate letermovir prophylaxis as a preventive strategy for CMV disease in kidney transplant recipients, the efficacy of letermovir was assessed in a multicentre, double-blind, active comparator-controlled non-inferiority Phase 3 trial (P002) in adult kidney transplant recipients at high risk [D+/R-]. Subjects were randomised (1:1) to receive either letermovir or valganciclovir. Letermovir was given concomitantly with acyclovir. Valganciclovir was given concomitantly with a placebo to acyclovir. Randomisation was stratified by the use or non-use of highly cytolytic, anti-lymphocyte immunotherapy during induction. Letermovir or valganciclovir were initiated between Day 0 and

Day 7 post-kidney transplant and continued through Week 28 (~200 days) post-transplant. Subjects were monitored through Week 52 post-transplant.

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

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

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

Table 6: P002: Efficacy results in kidney transplant recipients (OF approach, FAS population)

Parameter	Letermovir (N=289) n (%)	Valganciclovir (N=297) n (%)
CMV disease* through Week 52	**30 (10.4)**	**35 (11.8)**
Stratum-adjusted treatment difference (Letermovir-Valganciclovir)† Difference (95% CI)	-1.4 (-6.5, 3.8)‡	

* CMV disease cases confirmed by an independent adjudication committee.
† The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (use/non-use of highly cytolytic, anti-lymphocyte immunotherapy during induction).
‡ Based on a non-inferiority margin of 10%, letermovir is non-inferior to valganciclovir.
Approach to handling missing values: Observed Failure (OF) approach. With OF approach, participants who discontinue prematurely from the study for any reason are not considered failures.
Note: Subjects randomised to the letermovir group were given acyclovir for herpes simplex virus (HSV) and varicella zoster virus (VZV) prophylaxis. Subjects randomised to the valganciclovir group were given a placebo to acyclovir.
N=number of subjects in each treatment group.
n (%)=Number (percent) of subjects in each sub-category.

Efficacy was comparable across all subgroups, including sex, age, race, region, and the use/non-use of highly cytolytic, anti-lymphocyte immunotherapy during induction.

Paediatric population

P030: *Paediatric recipients of an allogeneic hematopoietic stem cell transplant*
To evaluate letermovir prophylaxis as a preventive strategy for CMV infection or disease in paediatric transplant recipients, the efficacy of letermovir was assessed in a multicentre, open-label, single-arm Phase 2b trial (P030) in paediatric recipients of an allogeneic HSCT. Study drug was initiated after HSCT (Day 0-28 post-HSCT) and continued through Week 14 post-HSCT. Study drug was administered either orally or intravenously; the dose of letermovir was based on age, body weight and formulation.

Among the 63 treated subjects, 8 were 0 to less than 2 years of age, 27 were 2 to less than 12 years of age and 28 were 12 to less than 18 years of age. At baseline, 87% of subjects received a myeloablative regimen, 67% were receiving cyclosporine, and 27% were receiving tacrolimus. The most common

primary reasons for transplant were acute myeloid leukaemia (18%) and aplastic anaemia (10%) in the overall population, and combined immunodeficiency (37.5%) and familial haemophagocytic lymphohistiocytosis (25.0%) in children less than 2 years of age.

Secondary efficacy endpoint
The efficacy endpoints of P030 were secondary and included the incidence of clinically significant CMV infection through Week 14 post-HSCT and through Week 24 post-HSCT. Clinically significant CMV infection was defined as the occurrence of either CMV end-organ disease, or initiation of anti-CMV PET based on documented CMV viremia and the clinical condition of the subject. The incidence of clinically significant CMV infection was 7.1% and 10.7% through Week 14 post-HSCT and Week 24 post-HSCT, respectively.

5.2 Pharmacokinetic properties

In healthy adult subjects, the pharmacokinetics of letermovir have been characterised following oral and intravenous administration. Letermovir exposure increased in a greater than dose-proportional manner with both oral or intravenous administration. The mechanism is likely saturation/autoinhibition of OATP1B1/3. The pharmacokinetics of letermovir have also been characterised following oral and intravenous administration in adult HSCT recipients (see Table 7) and paediatric HSCT recipients (see Table 9 and Table 10) and following oral administration in adult kidney transplant recipients (see Table 8).

Healthy adult 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 for C_{max}.

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

Table 7: Letermovir AUC (ng•hr/mL) values in adult HSCT Recipients

Treatment Regimen	Median (90% Prediction Interval)*
480 mg Oral, no cyclosporine	34 400 (16 900, 73 700)
480 mg intravenous, no cyclosporine	100 000 (65 300, 148 000)
240 mg Oral, with cyclosporine	60 800 (28 700, 122 000)
240 mg intravenous, with cyclosporine	70 300 (46 200, 106 000)
* Population post-hoc predictions from the population PK analysis using Phase 3 data	

Adult kidney transplant recipients
Letermovir AUC was estimated using population pharmacokinetic analysis using P002 Phase 3 data (see Table 8). Efficacy was consistent across the range of exposures observed in P002.

Table 8: Letermovir AUC (ng•hr/mL) values in adult kidney transplant recipients

Treatment Regimen	Median (90% Prediction Interval)*
480 mg Oral, no cyclosporine	62 200 (28 900, 145 000)
240 mg Oral, with cyclosporine	57 700 (26 900, 135 000)
* Medians and 90% prediction intervals are based on simulations using the Phase 3 population PK model with inter-individual variability. Note: PK of letermovir was not studied following intravenous administration in kidney transplant recipients; however, the projected AUC following intravenous administration is similar to the model predicted AUC following intravenous administration in HSCT recipients (see Table 7).	

Absorption

In healthy adult subjects, 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 adult 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%. In adult kidney transplant recipients, bioavailability of letermovir was estimated to be approximately 60% with 480 mg once daily oral letermovir administered without cyclosporine.

Effect of cyclosporine
In adult 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 in adult and paediatric patients weighing at least 30 kg (see section 4.2). If oral letermovir is co-administered with cyclosporine in paediatric patients weighing less than 30 kg, the dose should be decreased (see section 4.2).

Effect of food
In healthy adult subjects, oral administration of 480 mg single dose of letermovir tablet 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 tablets may be administered orally with or without food as has been done in the clinical trials (see section 4.2).

In healthy adult subjects, oral administration of 240 mg single dose of letermovir granules with soft foods (pudding or applesauce) resulted in an approximately 13% and 20% increase in overall exposure (AUC) and resulted in approximately 25% and 33% increase in peak levels (C_{max}) of letermovir. Letermovir granules may be administered with soft foods, as has been done in the paediatric trial (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 adult 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 intravenous letermovir in healthy adult 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 adult 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 adult 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 adult subjects. The changes in letermovir exposure in adult 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
Clinical study in a renally impaired population
Letermovir unbound AUC was approximately 115- and 81% higher in adult subjects with moderate (eGFR of 31 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 adult 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.

Post-kidney transplant (P002)
Based on population pharmacokinetic analysis, letermovir AUC was approximately 12%, 27% and 35% higher in adult subjects with mild (CrCl greater than or equal to 60 to less than 90 mL/min), moderate (CrCl greater than or equal to 30 to less than 60 mL/min) and severe (CrCl greater than or equal to 15 to less than 30 mL/min) renal impairment, respectively, compared to adult subjects with CrCl greater than or equal to 90 mL/min. These changes are not considered to be clinically relevant.

Weight
Based on population pharmacokinetic analyses in healthy adult subjects, letermovir AUC is estimated to be 18.7% lower in subjects weighing 80-100 kg compared to subjects weighing 67 kg. Based on population pharmacokinetic analysis in adult kidney transplant recipients (P002), letermovir AUC is estimated to be 26% lower in subjects weighing greater than 80 kg compared to subjects weighing less than or equal to 80 kg. These differences are not clinically relevant.

Race
Based on population pharmacokinetic analyses in healthy adult subjects, 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 adult 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.

Paediatric population
Letermovir AUC in paediatric HSCT recipients was estimated via population pharmacokinetic analysis using observed PK data from study P030 (see Table 9 and Table 10). Exposures for paediatric HSCT recipients across body weight bands are within the range of exposures achieved in the adult HSCT reference exposures (see Table 7).

Table 9: Letermovir AUC (ng•hr/mL) values following oral administration in paediatric HSCT recipients

Body weight	Oral dose, no cyclosporine	Median (90% prediction interval)*	Oral dose, with cyclosporine	Median (90% prediction interval)*
30 kg and above	480 mg	39 100 (18 700-81 300)	240 mg	49 100 (23 200-104 000)
15 kg to less than 30 kg	240 mg	38 900 (20 200-74 300)	120 mg	51 000 (26 600-98 200)
7.5 kg to less than 15 kg	120 mg	32 000 (16 700-59 300)	60 mg	41 600 (22 300-81 100)
5 kg to less than 7.5 kg	80 mg	30 600 (16 200-55 000)	40 mg	39 000 (20 600-72 000)
* Medians and 90% prediction intervals are based on simulations using the paediatric HSCT population PK model with inter-individual variability.				

Table 10: Letermovir AUC (ng•hr/mL) values following intravenous administration in paediatric HSCT recipients

Body weight	Intravenous dose, no cyclosporine	Median (90% prediction interval)*	Intravenous dose, with cyclosporine	Median (90% prediction interval)*
30 kg and above	480 mg	111 000 (55 700-218 000)	240 mg	59 800 (28 400-120 000)
15 kg to less than 30 kg	120 mg	57 200 (29 700-113 000)	120 mg	61 100 (29 900-121 000)
7.5 kg to less than 15 kg	60 mg	46 000 (24 300-83 900)	60 mg	49 200 (25 800-93 800)
5 kg to less than 7.5 kg	40 mg	43 400 (24 300-81 000)	40 mg	45 900 (24 900-82 200)
* Medians and 90% prediction intervals are based on simulations using the paediatric HSCT population PK model with inter-individual variability.				

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 characterised 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.

Carcinogenesis

A 6-month oral carcinogenicity study in RasH2 transgenic (Tg.RasH2) mice showed no evidence of human-relevant tumorigenesis up to the highest doses tested, 150 mg/kg/day and 300 mg/kg/day in males and females, respectively.

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

Microcrystalline cellulose (E460)
Croscarmellose sodium (E468)
Povidone (E1201)
Colloidal anhydrous silica (E551)
Magnesium stearate (E470b)
Lactose monohydrate
Hypromellose (E464)
Titanium dioxide (E171)
Triacetin
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Sachets consisting of Polyethylene terephthalate (PET)/Aluminum Foil/Linear low-density polyethylene (LLDPE) Each carton contains 30 sachets.

6.6 Special precautions for disposal and other handling

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

Preparation
PREVYMIS granules are administered orally mixed with soft food or via NG tube or G tube.

Preparation and administration mixed with soft food
See **Instructions for Use** for details on the preparation and administration of PREVYMIS granules mixed with soft food.

- Do not crush or chew PREVYMIS granules.
- Sprinkle PREVYMIS granules onto 1 to 3 teaspoons of soft food that is at or below room temperature. Do not use hot food. Examples of soft food include apple sauce or yoghurt.
- Mix PREVYMIS granules with the soft food.
- Administer entire mixture within 10 minutes of mixing PREVYMIS granules with the soft food.

Preparation and administration via NG tube or G tube
See **Instructions for Use**, Table 11 (NG tube) and Table 12 (G tube) for details on the preparation and administration of PREVYMIS granules via NG tube or G tube.

- Dispense initial volume of room temperature liquid (milk, apple juice, formula or water) into a medicine cup using the syringe. Do not mix PREVYMIS granules with water when

administering via G tube. Do not mix PREVYMIS granules with hot or cold (refrigerated) liquid.
- Pour PREVYMIS granules into the liquid in the medicine cup.
- Wait 10 minutes. Do not shake or swirl the medicine cup. PREVYMIS granules will not dissolve but will become loose or broken up.
- Stir the mixture with the syringe. Administer entire mixture using the syringe and NG tube or G tube.
- Dispense rinse volume of room temperature liquid (milk, apple juice, formula or water) into the medicine cup using the syringe. Do not rinse medicine cup with water when administering PREVYMIS via G tube.
- Stir the mixture with the syringe. Administer entire rinse mixture using the syringe and NG tube or G tube.
- Flush the NG tube or G tube with the volume of water recommended by the manufacturer.

Table 11: Recommendations for administration of PREVYMIS granules in sachet via NG tube

Dose	NG tube*	Liquid type	Syringe type†	Mixing container	Initial volume (mL)	Rinse volume (mL)
120 mg to 480 mg	Any ≥ 8 Fr NG tube	Milk, apple juice, formula, or water	Appropriately sized ENFit or catheter-tipped syringe	Medicine Cup	15	15
40 mg to 80 mg	5 Fr PUR NG tube or Any ≥ 6 Fr NG tube				3	2
* Fr = French; PUR = polyurethane † With ENFit syringe, a medicine straw (large bore) is needed to aid withdrawal of the mixture from the medicine cup.						

Table 12: Recommendations for administration of PREVYMIS granules in sachet via G tube

Dose	G tube*	Liquid type	Syringe type†	Mixing container	Initial volume (mL)	Rinse volume (mL)
120 mg to 480 mg	Any G tube	Milk, apple juice, or formula Do not use water	Appropriately sized ENFit or catheter-tipped syringe	Medicine Cup	15	15
40 mg to 80 mg	Any 12 Fr G tube				3	2
* Fr = French † With ENFit syringe, a medicine straw (large bore) is needed to aid withdrawal of the mixture from the medicine cup.						

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1245/005
EU/1/17/1245/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8 January 2018
Date of latest renewal: 24 August 2022

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release
Organon Heist bv
Industriepark 30
2220 Heist-op-den-Berg
Belgium

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

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSUR for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to optimise the sterility assurance level (SAL) of the manufacturing process, the marketing authorisation holder should implement the measures outlined in the Post Approval Change Management Protocol (PACMP) agreed with the CHMP concerning development, validation and introduction of terminal sterilisation.	31 March 2025 (PACMP Step 3)

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton for 240 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

PREVYMIS 240 mg film-coated tablets
letermovir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 240 mg of letermovir.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
28x1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
The tablets shall be swallowed whole with some water.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1245/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PREVYMIS 240 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

Blister for 240 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

PREVYMIS 240 mg tablets
letermovir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

MSD

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton for 480 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

PREVYMIS 480 mg film-coated tablets
letermovir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 480 mg of letermovir.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
28x1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
The tablets shall be swallowed whole with some water.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1245/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PREVYMIS 480 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

Blister for 480 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

PREVYMIS 480 mg tablets
letermovir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

MSD

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton for 240 mg concentrate for solution for infusion

1. NAME OF THE MEDICINAL PRODUCT

PREVYMIS 240 mg concentrate for solution for infusion
letermovir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 12 mL vial contains 240 mg letermovir.
Each mL contains 20 mg of letermovir.

3. LIST OF EXCIPIENTS

Contains sodium and cyclodextrin.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after dilution, **must be infused through an in-line filter.**
Single use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1245/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial label for 240 mg concentrate for solution for infusion

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PREVYMIS 240 mg sterile concentrate
letermovir
I.V., **must be infused through an in-line filter**.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MSD

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton for 480 mg concentrate for solution for infusion

1. NAME OF THE MEDICINAL PRODUCT

PREVYMIS 480 mg concentrate for solution for infusion
letermovir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 24 mL vial contains 480 mg of letermovir.
Each mL contains 20 mg of letermovir.

3. LIST OF EXCIPIENTS

Contains sodium and cyclodextrin.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after dilution, **must be infused through an in-line filter.**
Single use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1245/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial label for 480 mg concentrate for solution for infusion

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PREVYMIS 480 mg sterile concentrate
letermovir
I.V., **must be infused through an in-line filter.**

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MSD

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton for 20 mg granules in sachet

1. NAME OF THE MEDICINAL PRODUCT

PREVYMIS 20 mg granules in sachet
letermovir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet of granules contains 20 mg of letermovir.

3. LIST OF EXCIPIENTS

Contains lactose.

See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Granules in sachet

30 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Before use, read the package leaflet and instructions for use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1245/005

13. BATCH NUMBER<DONATION AND PRODUCT CODES>

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PREVYMIS 20 mg granules

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Sachet for 20 mg granules

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PREVYMIS 20 mg granules
letermovir

2. METHOD OF ADMINISTRATION

Oral use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MSD

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton for 120 mg granules in sachet

1. NAME OF THE MEDICINAL PRODUCT

PREVYMIS 120 mg granules in sachet
letermovir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet of granules contains 120 mg of letermovir.

3. LIST OF EXCIPIENTS

Contains lactose.

See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Granules in sachet

30 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Before use, read the package leaflet and instructions for use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1245/006

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PREVYMIS 120 mg granules

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Sachet for 120 mg granules

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PREVYMIS 120 mg granules
letermovir

2. METHOD OF ADMINISTRATION

Oral use

3. EXPIRY DATE

EXP

4. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MSD

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

PREVYMIS 240 mg film-coated tablets
PREVYMIS 480 mg film-coated tablets
letermovir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What PREVYMIS is and what it is used for
2. What you need to know before you take PREVYMIS
3. How to take PREVYMIS
4. Possible side effects
5. How to store PREVYMIS
6. Contents of the pack and other information

1. What PREVYMIS is and what it is used for

PREVYMIS is an antiviral prescription medicine that contains the active substance letermovir.

PREVYMIS is a medicine for:
- adults and children weighing at least 15 kg who have recently had a stem cell (bone marrow) transplant.
- adults and children weighing at least 40 kg who have recently had a kidney transplant.

The medicine helps stop you from getting ill from CMV ('cytomegalovirus').

CMV is a virus. For most people, CMV does not hurt them. However, if your immune system is weak after you get a stem cell transplant or a kidney transplant, you may be at high risk of becoming ill from CMV.

2. What you need to know before you take PREVYMIS

Do not take PREVYMIS if:
- you are allergic to letermovir or any of the other ingredients of this medicine (listed in section 6).
- you take either of these medicines:
  - pimozide - used for Tourette's syndrome
  - ergot alkaloids (such as ergotamine and dihydroergotamine) - used for migraine headaches.
- you take the following herbal product:
  - St. John's wort (Hypericum perforatum)

Do not take PREVYMIS if any of the above apply to you. If you are not sure, talk to your doctor, pharmacist or nurse before taking PREVYMIS.

If you are taking PREVYMIS with cyclosporine, do not take the following medicines:

- dabigatran - used for blood clots
- atorvastatin, simvastatin, rosuvastatin, pitavastatin - for high cholesterol

Warnings and precautions

If you are also taking a medicine for high cholesterol (see list of medicines in section "Other medicines and PREVYMIS" below) you must tell your doctor immediately if you have unexplained muscle aches or pains especially if you feel unwell or have a fever. Your medicine or dose may then need to be changed. See the package leaflet for your other medicine for further information.

Additional blood tests may be needed to monitor the following medicines:

- cyclosporine, tacrolimus, sirolimus
- voriconazole

Children and adolescents

PREVYMIS is not for use in children weighing less than 5 kg who have had a stem cell (bone marrow) transplant or in children weighing less than 40 kg who have had a kidney transplant. This is because PREVYMIS has not been tested in these groups.

Other medicines and PREVYMIS

Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. This is because PREVYMIS may affect the way other medicines work, and other medicines may affect how PREVYMIS works. Your doctor or pharmacist will tell you if it is safe to take PREVYMIS with other medicines.

There are some medicines you **must not take** with PREVYMIS (see list under "Do not take PREVYMIS if:").
There are some additional medicines you **must not take** with PREVYMIS and cyclosporine (see list under "If you are taking PREVYMIS with cyclosporine, do not take the following medicines:").

Also tell your doctor if you are taking any of the following medicines. This is because your doctor may have to change your medicines or change the dose of your medicines:

- alfentanil - for severe pain
- fentanyl - for severe pain
- quinidine - for abnormal heart rhythms
- cyclosporine, tacrolimus, sirolimus - used to prevent transplant rejection
- voriconazole - for fungal infections
- statins, such as atorvastatin, fluvastatin, rosuvastatin, simvastatin, pravastatin, pitavastatin - for high cholesterol
- glyburide, repaglinide - for high blood sugar
- carbamazepine, phenobarbital, phenytoin - for fits or seizures
- dabigatran, warfarin - used to thin the blood or for blood clots
- midazolam - used as a sedative
- amiodarone - used to correct irregular heartbeats
- oral contraceptive steroids - for birth control
- omeprazole, pantoprazole - for stomach ulcers and other stomach problems
- nafcillin - for bacterial infections
- rifabutin, rifampicin - for mycobacterial infections
- thioridazine - for psychiatric disorders
- bosentan - for high blood pressure in the vessels in the lungs
- efavirenz, etravirine, nevirapine, lopinavir, ritonavir - for HIV
- modafinil - for wakefulness

You can ask your doctor or pharmacist for a list of medicines that may interact with PREVYMIS.

Pregnancy
If you are pregnant, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before taking this medicine. PREVYMIS is not recommended in pregnancy. This is because it has not been studied in pregnancy and it is not known if PREVYMIS will harm your baby while you are pregnant.

Breast-feeding
If you are breast-feeding or are planning to breast-feed, tell your doctor before taking this medicine. Breast-feeding is not recommended while taking PREVYMIS. This is because it is not known if PREVYMIS gets in your breast milk and will be passed to your baby.

Driving and using machines
PREVYMIS may have minor influence on your ability to drive and use machines (see section 4 "Possible side effects" below). Some patients have reported fatigue (feeling very tired) or vertigo (feeling like you are spinning) during treatment with PREVYMIS. If you experience any of these effects, do not drive or use machines until the effect wears off.

PREVYMIS contains lactose
PREVYMIS contains lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

PREVYMIS contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take PREVYMIS

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
Your dose of PREVYMIS depends on how much you weigh and if you are also taking cyclosporine. Your doctor will tell you how many tablets to take.
- Take PREVYMIS as directed once a day.
- Take PREVYMIS at the same time every day.
- Take it with or without food.

The recommended oral doses of PREVYMIS are provided in Table 1 and Table 2.

Table 1: The recommended doses of PREVYMIS film-coated tablets without cyclosporine

Weight	PREVYMIS daily oral dose	Number of PREVYMIS tablets once daily
30 kg and above	480 mg	One 480 mg tablet or Two 240 mg tablets
15 kg to less than 30 kg	240 mg	One 240 mg tablet

Table 2: The recommended doses of PREVYMIS film-coated tablets with cyclosporine

Weight	PREVYMIS daily oral dose	Number of PREVYMIS tablets once daily
30 kg and above	240 mg	One 240 mg tablet
15 kg to less than 30 kg	120 mg	Refer to PREVYMIS granules in sachet package leaflet

How to take
- Swallow the tablet whole with some water. Do not break, crush, or chew the tablet because these methods have not been studied.

If you take more PREVYMIS than you should
If you take more PREVYMIS than you should, call your doctor straight away.

If you forget to take PREVYMIS
It is very important that you do not miss or skip doses of PREVYMIS.
- If you forget a dose, take it as soon as you remember. However, if it is nearly time for the next dose, skip the missed dose. Take your next dose at the 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.

Do not stop taking PREVYMIS
Do not stop taking PREVYMIS without talking to your doctor first. Do not run out of PREVYMIS. This will give the medicine the best chance to keep you from becoming ill from CMV after you get a stem cell transplant or a kidney transplant.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Common: may affect up to 1 in 10 people
- diarrhoea
- feeling sick (nausea)
- being sick (vomiting)

Uncommon: may affect up to 1 in 100 people
- allergic reaction (hypersensitivity) – the signs may include wheezing, difficulty breathing, rashes or hives, itchiness, swelling
- loss of appetite
- changes in taste
- headache
- feeling like you are spinning (vertigo)
- stomach ache
- abnormalities in laboratory tests of liver function (i.e., raised levels of liver enzymes)
- muscle spasms
- high blood creatinine - shown in blood tests
- feeling very tired (fatigue)
- swelling of hands or feet

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store PREVYMIS

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister card after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special temperature storage conditions. Store in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What PREVYMIS contains
The active substance is letermovir. Each film-coated tablet contains 240 mg letermovir or 480 mg letermovir.

The other ingredients are:

Tablet core

Microcrystalline cellulose (E460), croscarmellose sodium (E468), povidone (E1201), colloidal anhydrous silica (E551), magnesium stearate (E470b).

Film-coating

Lactose monohydrate, hypromellose (E464), titanium dioxide (E171), triacetin, iron oxide yellow (E172), iron oxide red (only for 480 mg tablets) (E172), carnauba wax (E903). See section 2 "PREVYMIS contains lactose" and "PREVYMIS contains sodium".

What PREVYMIS looks like and contents of the pack
PREVYMIS 240 mg film-coated tablet ("tablet") is a yellow oval tablet, debossed with "591" on one side and corporate logo on the other side. The tablet is 16.5 mm long and 8.5 mm wide.

PREVYMIS 480 mg film-coated tablet ("tablet") is a pink oval, bi-convex tablet, debossed with "595" on one side and corporate logo on the other side. The tablet is 21.2 mm long and 10.3 mm wide.

The 28x1 tablets are packaged into a carton containing Polyamide/Aluminium/PVC – Aluminium perforated unit dose blister cards (total of 28 tablets).

Marketing Authorisation Holder
Merck Sharp & Dohme B.V.
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2031 BN Haarlem
The Netherlands

Manufacturer
Organon Heist bv
Industriepark 30
2220 Heist-op-den-Berg
Belgium

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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in {**MM/YYYY**}.

Detailed information on this medicine is available on the European Medicines Agency website: https://www.ema.europa.eu .

Package leaflet: Information for the patient

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

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What PREVYMIS is and what it is used for
2. What you need to know before you are given PREVYMIS
3. How you are given PREVYMIS
4. Possible side effects
5. How to store PREVYMIS
6. Contents of the pack and other information

1. What PREVYMIS is and what it is used for

PREVYMIS is an antiviral prescription medicine that contains the active substance letermovir.

PREVYMIS is a medicine for:
- adults and children weighing at least 5 kg who have recently had a stem cell (bone marrow) transplant.
- adults and children weighing at least 40 kg who have recently had a kidney transplant.

The medicine helps stop you from getting ill from CMV ('cytomegalovirus').

CMV is a virus. For most people, CMV does not hurt them. However, if your immune system is weak after you get a stem cell transplant or a kidney transplant, you may be at high risk of becoming ill from CMV.

2. What you need to know before you are given PREVYMIS

You should not be given PREVYMIS if:
- you are allergic to letermovir or any of the other ingredients of this medicine (listed in section 6).
- you take either of these medicines:
  - pimozide - used for Tourette's syndrome
  - ergot alkaloids (such as ergotamine and dihydroergotamine) - used for migraine headaches.
- you take the following herbal product:
  - St. John's wort (Hypericum perforatum)

You should not be given PREVYMIS if any of the above apply to you. If you are not sure, talk to your doctor, pharmacist or nurse before you are given PREVYMIS.

If you are taking PREVYMIS with cyclosporine, do not take the following medicines:
- dabigatran - used for blood clots
- atorvastatin, simvastatin, rosuvastatin, pitavastatin –for high cholesterol

Warnings and precautions
If you are also taking a medicine for high cholesterol (see list of medicines in section "Other medicines and PREVYMIS" below) you must tell your doctor immediately if you have unexplained muscle aches or pains especially if you feel unwell or have a fever. Your medicine or dose may then need to be changed. See the package leaflet for your other medicine for further information.

Additional blood tests may be needed to monitor the following medicines :
- cyclosporine, tacrolimus, sirolimus
- voriconazole

Children and adolescents
PREVYMIS is not for use in children weighing less than 5 kg who have had a stem cell (bone marrow) transplant or in children weighing less than 40 kg who have had a kidney transplant. This is because PREVYMIS has not been tested in these groups.

Other medicines and PREVYMIS
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. This is because PREVYMIS may affect the way other medicines work, and other medicines may affect how PREVYMIS works. Your doctor or pharmacist will tell you if it is safe to take PREVYMIS with other medicines.

There are some medicines you **must not take** with PREVYMIS (see list under "You should not be given PREVYMIS if:").
There are some additional medicines you **must not take** with PREVYMIS and cyclosporine (see list under "If you are taking PREVYMIS with cyclosporine, do not take the following medicines:").

Also tell your doctor if you are taking any of the following medicines. This is because your doctor may have to change your medicines or change the dose of your medicines:
- alfentanil - for severe pain
- fentanyl - for severe pain
- quinidine - for abnormal heart rhythms
- cyclosporine, tacrolimus, sirolimus - used to prevent transplant rejection
- voriconazole - for fungal infections
- statins, such as atorvastatin, fluvastatin, rosuvastatin, simvastatin, pravastatin, pitavastatin - for high cholesterol
- glyburide, repaglinide - for high blood sugar
- carbamazepine, phenobarbital, phenytoin - for fits or seizures
- dabigatran, warfarin - used to thin the blood or for blood clots
- midazolam - used as a sedative
- amiodarone - used to correct irregular heartbeats
- oral contraceptive steroids - for birth control
- omeprazole, pantoprazole - for stomach ulcers and other stomach problems
- nafcillin - for bacterial infections
- rifabutin, rifampicin - for mycobacterial infections
- thioridazine - for psychiatric disorders
- bosentan - for high blood pressure in the vessels in the lungs
- efavirenz, etravirine, nevirapine, lopinavir, ritonavir - for HIV
- modafinil - for wakefulness

You can ask your doctor or pharmacist for a list of medicines that may interact with PREVYMIS.

Pregnancy
If you are pregnant, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before taking this medicine. PREVYMIS is not recommended in pregnancy. This is because it has not been studied in pregnancy and it is not known if PREVYMIS will harm your baby while you are pregnant.

Breast-feeding
If you are breast-feeding or are planning to breast-feed, tell your doctor before taking this medicine. Breast-feeding is not recommended while taking PREVYMIS. This is because it is not known if PREVYMIS gets in your breast milk and will be passed to your baby.

Driving and using machines
PREVYMIS may have minor influence on your ability to drive and use machines (see section 4 Possible side effects below). Some patients have reported fatigue (feeling very tired) or vertigo (feeling like you are spinning) during treatment with PREVYMIS. If you experience any of these effects, do not drive or use machines until the effect wears off.

PREVYMIS contains sodium
PREVYMIS contains sodium. If you are on a low sodium diet, talk to your doctor before you are given this medicine.

Each 240 mg vial contains 23 mg sodium (main component of cooking/table salt). This is equivalent to 1.15% of the recommended maximum daily dietary intake of sodium for an adult.

Each 480 mg vial contains 46 mg sodium (main component of cooking/table salt). This is equivalent to 2.30% of the recommended maximum daily dietary intake of sodium for an adult.

PREVYMIS contains cyclodextrin
Each 40 mg dose of this medicine contains 300 mg cyclodextrin.
Each 60 mg dose of this medicine contains 450 mg cyclodextrin.
Each 120 mg dose of this medicine contains 900 mg cyclodextrin.
Each 240 mg dose of this medicine contains 1 800 mg cyclodextrin.
Each 480 mg dose of this medicine contains 3 600 mg cyclodextrin.

If you have a kidney disease, talk to your doctor before you receive this medicine.

3. How you are given PREVYMIS

Your dose of PREVYMIS depends on how much you weigh and if you are also taking cyclosporine.
Your doctor will decide on the correct dose of PREVYMIS.
You will get PREVYMIS as an infusion (drip) into a vein and it will take about 1 hour.
You will get PREVYMIS once a day.

The recommended intravenous doses of PREVYMIS are provided in Table 1.

Table 1: The recommended dose of PREVYMIS concentrate for solution for infusion without or with cyclosporine

Weight	**Daily intravenous dose without cyclosporine**	**Daily intravenous dose with cyclosporine**
30 kg and above	480 mg	240 mg
Weight	**Daily intravenous dose without or with cyclosporine**	
15 kg to less than 30 kg	120 mg	
7.5 kg to less than 15 kg	60 mg	
5 kg to less than 7.5 kg	40 mg	

If you are given more PREVYMIS than you should
If you think you have been given too much PREVYMIS, tell your doctor straight away.

If you miss your appointment to get PREVYMIS
It is very important that you do not miss or skip doses of PREVYMIS.
- If you miss your appointment to get PREVYMIS, call your doctor straight away to reschedule your appointment.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Common: may affect up to 1 in 10 people
- diarrhoea
- feeling sick (nausea)
- being sick (vomiting)

Uncommon: may affect up to 1 in 100 people
- allergic reaction (hypersensitivity) – the signs may include wheezing, difficulty breathing, rashes or hives, itchiness, swelling
- loss of appetite
- changes in taste
- headache
- feeling like you are spinning (vertigo)
- stomach ache
- abnormalities in laboratory tests of liver function (i.e., raised levels of liver enzymes)
- muscle spasms
- high blood creatinine - shown in blood tests
- feeling very tired (fatigue)
- swelling of hands or feet

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store PREVYMIS

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special temperature storage conditions. Store in original carton to protect from light.

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.

Any unused portion of the infusion solution should be discarded.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What PREVYMIS contains
The active substance is letermovir. Each vial contains 240 mg or 480 mg letermovir. Each mL of concentrate contains 20 mg.
The other ingredients are: hydroxypropylbetadex (cyclodextrin), sodium chloride, sodium hydroxide (E524), water for injections. See section 2 “PREVYMIS contains sodium” and “PREVYMIS contains cyclodextrin”.

What PREVYMIS looks like and contents of the pack
PREVYMIS 240 mg and 480 mg concentrate for solution for infusion (sterile concentrate) is a clear, colourless liquid and may contain a few product-related small translucent or white particles.
The 240 mg and 480 mg concentrate for solution for infusion is packaged in clear, glass vials. Each vial is packaged in a carton.

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This leaflet was last revised in {**MM/YYYY**}.

Detailed information on this medicine is available on the European Medicines Agency website: https://www.ema.europa.eu .

The following information is intended for healthcare professionals only:

Administration instructions for PREVYMIS concentrate for solution for infusion

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

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.

Preparation

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 intravenous 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.
- For the **480 mg or 240 mg dose**, 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 intravenous bag containing either 0.9% sodium chloride or 5% dextrose, and mix the diluted solution by gentle inversion. Do not shake. If a vial is added to a 250 mL intravenous 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).
  For the **120 mg or 60 mg dose**, prepare PREVYMIS concentrate for solution for infusion according to Table 1 below in sodium chloride 9 mg/mL (0.9%) or 5% dextrose, and mix the diluted solution by gentle inversion. Do not shake.
  For the **40 mg dose**, prepare PREVYMIS concentrate for solution for infusion according to Table 2 below in sodium chloride 9 mg/mL (0.9%) or 5% dextrose, and mix the diluted solution by gentle inversion. Do not shake.

Table 1: Preparation of PREVYMIS intravenous solution for doses of 120 mg or 60 mg

Intravenous dose	Volume of 20 mg/mL PREVYMIS concentrate for solution for infusion	Final infusion volume	Final concentration of letermovir
120 mg	6 mL of 20 mg/mL	75 mL	1.6 mg/mL
60 mg	3 mL of 20 mg/mL	50 mL	1.2 mg/mL

Table 2: Preparation of PREVYMIS intravenous solution for a dose of 40 mg

Intravenous dose	Volume of 2 mg/mL PREVYMIS dilution (1:10)*	Final infusion volume	Final concentration of letermovir
40 mg	20 mL of 2 mg/mL	20 mL	2 mg/mL
* To prepare 2 mg/mL PREVYMIS dilution, add 5 mL of 20 mg/mL PREVYMIS concentrate for solution for infusion from the vial to 45 mL of diluent (sodium chloride 9 mg/mL (0.9%) or 5% dextrose) and mix gently.			

- 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.

Administration

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

Compatible intravenous solutions and other medicinal products

- PREVYMIS concentrate for solution for infusion is compatible with 0.9% sodium chloride and 5% dextrose solutions.
- Compatible medicinal products are listed below.
- This medicinal product must not be mixed with other medicinal products except those listed below.
- 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

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 sulphate, levofloxacin, linezolid, lorazepam, midazolam HCl, mycophenolate mofetil hydrochloride, ondansetron, palonosetron.

Incompatible intravenous bags and infusion set materials

PREVYMIS is incompatible with diethylhexyl phthalate (DEHP) plasticizers and polyurethane-containing intravenous administration set tubing.

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

Package leaflet: Information for the patient

PREVYMIS 20 mg granules in sachet
PREVYMIS 120 mg granules in sachet
letermovir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What PREVYMIS is and what it is used for
2. What you need to know before you take PREVYMIS
3. How to take PREVYMIS
4. Possible side effects
5. How to store PREVYMIS
6. Contents of the pack and other information

1. What PREVYMIS is and what it is used for

PREVYMIS is an antiviral prescription medicine that contains the active substance letermovir.

PREVYMIS is a medicine for:
- adults and children weighing at least 5 kg who have recently had a stem cell (bone marrow) transplant.
- adults and children weighing at least 40 kg who have recently had a kidney transplant.

The medicine helps stop you from getting ill from CMV (‘cytomegalovirus’).

CMV is a virus. For most people, CMV does not hurt them. However, if your immune system is weak after you get a stem cell transplant or a kidney transplant, you may be at high risk of becoming ill from CMV.

2. What you need to know before you take PREVYMIS

Do not take PREVYMIS if:
- you are allergic to letermovir or any of the other ingredients of this medicine (listed in section 6).
- you take either of these medicines:
  - pimozide - used for Tourette’s syndrome
  - ergot alkaloids (such as ergotamine and dihydroergotamine) - used for migraine headaches.
- you take the following herbal product:
  - St. John’s wort (*Hypericum perforatum*)

Do not take PREVYMIS if any of the above apply to you. If you are not sure, talk to your doctor, pharmacist or nurse before taking PREVYMIS.

If you are taking PREVYMIS with cyclosporine, do not take the following medicines:
- dabigatran - used for blood clots
- atorvastatin, simvastatin, rosuvastatin, pitavastatin – for high cholesterol

Warnings and precautions
If you are also taking a medicine for high cholesterol (see list of medicines in section "Other medicines and PREVYMIS" below) you must tell your doctor immediately if you have unexplained muscle aches or pains especially if you feel unwell or have a fever. Your medicine or dose may then need to be changed. See the package leaflet for your other medicine for further information.

Additional blood tests may be needed to monitor the following medicines:
- cyclosporine, tacrolimus, sirolimus
- voriconazole

Children and adolescents
PREVYMIS is not for use in children weighing less than 5 kg who have had a stem cell (bone marrow) transplant or in children weighing less than 40 kg who have had a kidney transplant. This is because PREVYMIS has not been tested in these groups.

Other medicines and PREVYMIS
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. This is because PREVYMIS may affect the way other medicines work, and other medicines may affect how PREVYMIS works. Your doctor or pharmacist will tell you if it is safe to take PREVYMIS with other medicines.

There are some medicines you **must not take** with PREVYMIS (see list under "Do not take PREVYMIS if:").
There are some additional medicines you **must not take** with PREVYMIS and cyclosporine (see list under "If you are taking PREVYMIS with cyclosporine, do not take the following medicines:").

Also tell your doctor if you are taking any of the following medicines. This is because your doctor may have to change your medicines or change the dose of your medicines:
- alfentanil - for severe pain
- fentanyl - for severe pain
- quinidine - for abnormal heart rhythms
- cyclosporine, tacrolimus, sirolimus - used to prevent transplant rejection
- voriconazole - for fungal infections
- statins, such as atorvastatin, fluvastatin, rosuvastatin, simvastatin, pravastatin, pitavastatin – for high cholesterol
- glyburide, repaglinide - for high blood sugar
- carbamazepine, phenobarbital, phenytoin - for fits or seizures
- dabigatran, warfarin - used to thin the blood or for blood clots
- midazolam - used as a sedative
- amiodarone - used to correct irregular heartbeats
- oral contraceptive steroids - for birth control
- omeprazole, pantoprazole - for stomach ulcers and other stomach problems
- nafcillin - for bacterial infections
- rifabutin, rifampicin - for mycobacterial infections
- thioridazine - for psychiatric disorders
- bosentan - for high blood pressure in the vessels in the lungs
- efavirenz, etravirine, nevirapine, lopinavir, ritonavir - for HIV
- modafinil - for wakefulness

You can ask your doctor or pharmacist for a list of medicines that may interact with PREVYMIS.

Pregnancy
If you are pregnant, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before taking this medicine. PREVYMIS is not recommended in pregnancy. This is because it has not been studied in pregnancy and it is not known if PREVYMIS will harm your baby while you are pregnant.

Breast-feeding
If you are breast-feeding or are planning to breast-feed, tell your doctor before taking this medicine. Breast-feeding is not recommended while taking PREVYMIS. This is because it is not known if PREVYMIS gets in your breast milk and will be passed to your baby.

Driving and using machines
PREVYMIS may have minor influence on your ability to drive and use machines (see section 4 "Possible side effects" below). Some patients have reported fatigue (feeling very tired) or vertigo (feeling like you are spinning) during treatment with PREVYMIS. If you experience any of these effects, do not drive or use machines until the effect wears off.

PREVYMIS contains lactose
PREVYMIS contains lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

PREVYMIS contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per sachet, that is to say essentially 'sodium-free'.

3. How to take PREVYMIS

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
Your dose of PREVYMIS depends on how much you weigh and if you are also taking cyclosporine. Your doctor will tell you the number of sachets to take.
- Take PREVYMIS as directed once a day.

The recommended oral doses of PREVYMIS are provided in Table 1 and Table 2.

Table 1: The recommended doses of PREVYMIS granules in sachet without cyclosporine

Weight	PREVYMIS daily oral dose	Number of PREVYMIS sachets once daily
30 kg and above	480 mg	Four 120 mg sachets
15 kg to less than 30 kg	240 mg	Two 120 mg sachets
7.5 kg to less than 15 kg	120 mg	One 120 mg sachet
5 kg to less than 7.5 kg	80 mg	Four 20 mg sachets

Table 2: The recommended doses of PREVYMIS granules in sachet with cyclosporine

Weight	PREVYMIS daily oral dose	Number of PREVYMIS sachets once daily
30 kg and above	240 mg	Two 120 mg sachets
15 kg to less than 30 kg	120 mg	One 120 mg sachet
7.5 kg to less than 15 kg	60 mg	Three 20 mg sachets
5 kg to less than 7.5 kg	40 mg	Two 20 mg sachets

How to take
- See **Instructions for Use** for the right way to prepare and take a dose of PREVYMIS. Keep the Instructions for Use and follow it each time you prepare and take the medicine.

- Contact your doctor if you have any questions about how to take PREVYMIS.

If you take more PREVYMIS than you should
If you take more PREVYMIS than you should, call your doctor straight away.

If you forget to take PREVYMIS
It is very important that you do not miss or skip doses of PREVYMIS.
- If you forget a dose, take it as soon as you remember. However, if it is nearly time for the next dose, skip the missed dose. Take your next dose at the usual time.
- Do not take two doses of PREVYMIS at the same time to make up for a missed dose.
- If you miss a dose, do not take the full dose, or spit some up, call your doctor.
- If you are not sure what to do, call your doctor or pharmacist.

Do not stop taking PREVYMIS
Do not stop taking PREVYMIS without talking to your doctor first. Do not run out of PREVYMIS. This will give the medicine the best chance to keep you from becoming ill from CMV after you get a stem cell transplant or a kidney transplant.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Common: may affect up to 1 in 10 people
- diarrhoea
- feeling sick (nausea)
- being sick (vomiting)

Uncommon: may affect up to 1 in 100 people
- allergic reaction (hypersensitivity) – the signs may include wheezing, difficulty breathing, rashes or hives, itchiness, swelling
- loss of appetite
- changes in taste
- headache
- feeling like you are spinning (vertigo)
- stomach ache
- abnormalities in laboratory tests of liver function (i.e., raised levels of liver enzymes)
- muscle spasms
- high blood creatinine - shown in blood tests
- feeling very tired (fatigue)
- swelling of hands or feet

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store PREVYMIS

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and sachet after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What PREVYMIS contains

PREVYMIS 20 mg granules in sachet:
The active substance is letermovir. Each sachet contains 20 mg of letermovir.

PREVYMIS 120 mg granules in sachet:
The active substance is letermovir. Each sachet contains 120 mg of letermovir.

The other ingredients are: Microcrystalline cellulose (E460), croscarmellose sodium (E468), povidone (E1201), colloidal anhydrous silica (E551), magnesium stearate (E470b), lactose monohydrate, hypromellose (E464), titanium dioxide (E171), triacetin, iron oxide yellow (E172), iron oxide red (E172).

See section 2 “PREVYMIS contains lactose” and “PREVYMIS contains sodium”.

What PREVYMIS looks like and contents of the pack

PREVYMIS 20 mg granules in sachet are beige granules.
PREVYMIS 120 mg granules in sachet are beige granules.

The granules are supplied in sachets.
- Pack size of 30 sachets.

Marketing Authorisation Holder and Manufacturer
Merck Sharp & Dohme B.V.
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This leaflet was last revised in {**MM/YYYY**}.

Detailed information on this medicine is available on the European Medicines Agency website: https://www.ema.europa.eu .

Instructions for Use
Important: read this booklet first

PREVYMIS 20 mg granules in sachet
PREVYMIS 120 mg granules in sachet

letermovir

This “Instructions for Use” contains information on how to take PREVYMIS

Important information you need to know before taking PREVYMIS

- Take PREVYMIS by mouth (orally) or give by feeding tube.
  - **Do not** crush or chew PREVYMIS.
- When to take:
  - Take the medicine around the same time every day.
- How much to take:
  - Your doctor will tell you the right amount (dose) for you, based on your weight and if you are also taking cyclosporine.
  - Take the full dose each time.
  - Keep your doctor visits since your dose may change.

Call your doctor if you miss a dose, do not take the full dose, or spit some up.

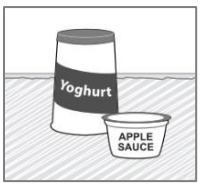
How to take PREVYMIS
Talk to your doctor about which way to take this medicine.

Follow **ONE** of these ways to take PREVYMIS:

- Mix with soft food – Go to “Mix with soft food” section.

- Give through a feeding tube – Go to “Give through a feeding tube” section.

Mix with soft food



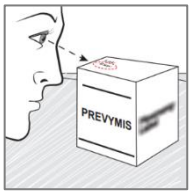
Important information about mixing PREVYMIS with soft food

- Only use room temperature or cold food.
  - **Do not** use hot food.

- Timing is important! Before you start, make sure you are ready!
  - You must take all of the mixture within 10 minutes of mixing PREVYMIS with the food.

Mix with soft food

Step 1: Wash your hands with soap and water, dry your hands.

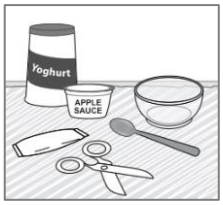


Step 2: Check the expiry date located on the top of the carton.

- **Do not** use if PREVYMIS is expired.

Mix with soft food

Note: Your doctor will tell you the number of sachets needed for your dose.



Step 3: Gather all your supplies on a clean surface.

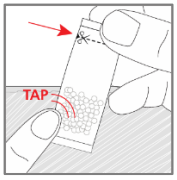
- The number of sachets as advised by your doctor
- Scissors
- Small bowl
- Teaspoon (small spoon)

Step 4: Pick a soft food that you enjoy, such as apple sauce or yoghurt.

- **Do not** use hot food.

Mix with soft food

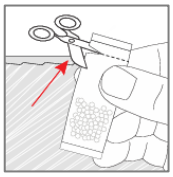
Step 5: Put 1 to 3 teaspoons (small spoons) of soft food into the small bowl.



Step 6: Tap the sachet(s) to loosen the granules to the bottom of the sachet(s).

- Hold the sachet(s) with the dotted line at the top.

Mix with soft food



Step 7: Cut open the sachet(s) with scissors at the dotted line.

Step 8: Lightly tap the sachet(s) to carefully sprinkle all the granules onto the soft food in the same small bowl.

- Make sure all of the granules go into the small bowl.
- Make sure the sachet(s) is empty.
- If any granules spill, call your doctor.

Mix with soft food

Step 9: Use the spoon to gently mix the food and PREVYMIS together.

Mix with soft food

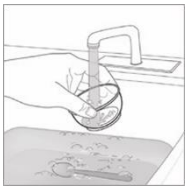
Step 10: Take ALL of the PREVYMIS mixture.

- When finished, check that no granules are left in the bowl or on the spoon.
- If you are hungry, you can eat more food or a meal afterwards.

If your do not finish all of the PREVYMIS mixture or spit some up, call your doctor.

Timing is important! Your child should eat all of the mixture within 10 minutes of mixing PREVYMIS with the food.

Mix with soft food



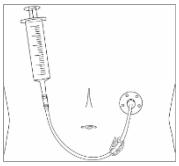
Step 11: Clean up.

- Throw the empty sachet(s) into the trash.
- Wash the small bowl and spoon with soap and water.
- Put everything in a clean, dry place.

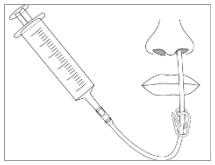
For further information, go to sections “How to store PREVYMIS sachets” and “Learn more about PREVYMIS.”

Give through a feeding tube

These instructions are only for patients with a feeding tube.



Gastric tube (G tube)



Nasogastric tube (NG tube)

Ask your doctor how to give PREVYMIS through a feeding tube and how to clean the feeding tube.

Give through a feeding tube

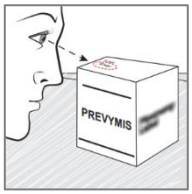
Important information about mixing PREVYMIS with liquid

- PREVYMIS should be mixed with milk, apple juice, or infant formula (IF). PREVYMIS may also be mixed with water, but only when PREVYMIS is given through an NG tube.
  - Allow liquids to reach room temperature.
  - **Do not** mix PREVYMIS with hot or cold (refrigerated) liquid.

- Timing is important! Before you start, make sure you are ready!
  - After you mix PREVYMIS with liquid, you must wait at least 10 minutes before giving it. This allows the granules to break apart so they do not block the feeding tube.
  - Once it is ready, **immediately** follow steps to give the mixture.

Give through a feeding tube

Step 1: Wash your hands with soap and water, dry your hands.



Step 2: Check the expiry date located on the top of the carton.

- **Do not** use if PREVYMIS is expired.

Give through a feeding tube

Note: Your doctor will tell you the number of sachets needed for your dose.

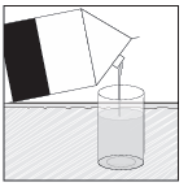
Step 3: Gather all your supplies on a clean surface.

- The number of sachets as advised by your doctor
- Scissors
- Clock or timer
- Small household glass
- Feeding tube syringe provided by your doctor or pharmacist
- Medicine cup (15 to 30 mL) provided by your doctor or pharmacist

Give through a feeding tube

Step 4: Pick a liquid: milk, apple juice, or infant formula (IF).

- Water may also be used, but only when PREVYMIS is given through an NG tube.



Step 5: Pour a small amount of the liquid into the glass.

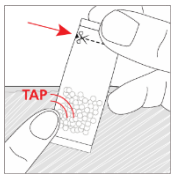
- Allow liquids to reach room temperature.
- **Do not** use hot or cold (refrigerated) liquid.

Step 6: Pull up on the syringe plunger to collect liquid from the glass into the syringe.

- Your doctor will tell you how much liquid to use.

Give through a feeding tube

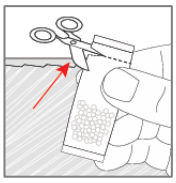
Step 7: Empty the liquid from the syringe into the small, clean medicine cup.



Step 8: Tap the sachet(s) to loosen the granules to the bottom of the sachet(s).

- Hold the sachet(s) with the dotted line at the top.

Give through a feeding tube



Step 9: Cut open the sachet(s) with scissors at the dotted line.

Step 10: Lightly tap the sachet(s) to carefully pour into the same medicine cup.

- Make sure all of the granules go into the medicine cup.
- Make sure the sachet(s) is empty.
- If any granules spill, call your doctor.

Give through a feeding tube

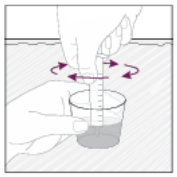
Step 11: Use a clock or timer and wait 10 minutes.

- **Do not** shake or swirl the medicine cup

Important: While waiting, keep the medicine cup in a safe place out of reach of children.

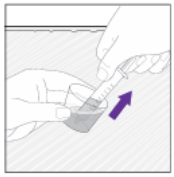
- PREVYMIS will not dissolve but will become loose or broken up.
- After 10 minutes, the mixture will be ready to use.
- Once it is ready, follow Steps 12-19 to give the mixture.

Give through a feeding tube



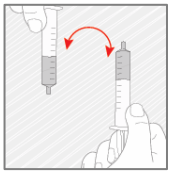
Step 12: Gently stir the mixture with the syringe tip.

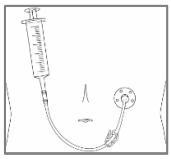
- **Do not** shake or swirl the medicine cup.

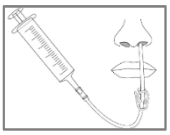


Step 13: Tilt the medicine cup and pull up on the syringe plunger to collect all of the mixture from the medicine cup.

Give through a feeding tube







Step 14: Give the PREVYMIS mixture.

- Gently invert the syringe to keep the medicine from settling.
  - **Do not** shake the syringe since this can cause air bubbles.
- Attach the syringe to the feeding tube.
- Slowly push on the plunger to move the mixture through the feeding tube.

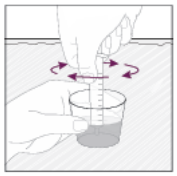
Give through a feeding tube

Step 15: To rinse, use the same syringe and pull up on the syringe plunger to collect liquid from the same glass.

- Your doctor will tell you how much liquid to use.

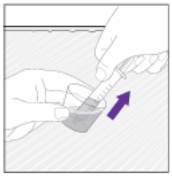
Step 16: Slowly push on the plunger to add the liquid in the syringe to the same medicine cup.

Give through a feeding tube



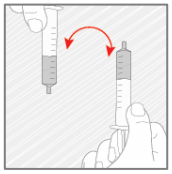
Step 17: Gently stir the mixture with the syringe tip.

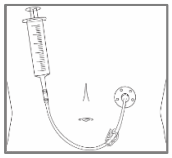
- **Do not** shake or swirl the medicine cup.

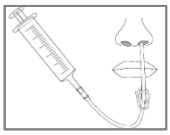


Step 18: Tilt the medicine cup and pull up on the syringe plunger to collect the all of the mixture from the medicine cup.

Give through a feeding tube







Step 19: Give the rinse mixture.

- Gently invert the syringe to keep the medicine from settling.
  - **Do not** shake the syringe since this can cause air bubbles.
- Attach the syringe to the feeding tube.
- Slowly push on the plunger to move the mixture through the feeding tube.

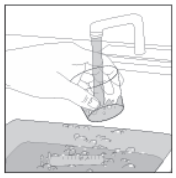
If all of the PREVYMIS mixture is not finished, call your doctor.

Give through a feeding tube

Step 20: Flush the feeding tube right away using water.

- Ask your doctor how much water to use.

Give through a feeding tube



Step 21: Clean up

- Throw the empty sachet(s) into the trash.
- Hand wash the syringe and medicine cup with warm water and dish soap.
  - **Do not** wash the syringe and medicine cup in the dishwasher.
  - **Do not** boil the syringe and medicine cup.
- Put everything in a clean, dry place.

For further information, go to sections “How to store PREVYMIS sachets” and “Learn more about PREVYMIS”.

How to store PREVYMIS sachets

- PREVYMIS does not require any special storage conditions.
- Keep this and all medicine out of the reach of children.

Learn more about PREVYMIS
For more information on how to use PREVYMIS, ask your doctor or your pharmacist and read the PREVYMIS package leaflet.