SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

PREVYMIS® 240 mg Film-coated Tablets

PREVYMIS® 240 mg Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

PREVYMIS 240 mg Film-coated Tablets

Each film-coated tablet contains 240 mg of letermovir.

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.

Excipient with known effect

PREVYMIS 240 mg Film-coated Tablets

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

Each 240 mg film-coated tablet contains < 1 mmoL sodium (23 mg).

PREVYMIS 240 mg Concentrate for Solution for Infusion

This medicinal product contains 23 mg (1,0 mmoL) sodium per 240 mg vial, equivalent to 1,15 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Each 240 mg dose (12 mL vial) of this medicinal product contains 1 800 mg hydroxypropylbetadex (cyclodextrin).

Each 480 mg dose (two 12 mL vials) of this medicinal product contains 3 600 mg hydroxypropylbetadex (cyclodextrin).

For additional information, see section 4.2.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Yellow oval tablet of dimensions 16,5 mm x 8,5 mm, debossed with “591” on one side and MSD logo on the other side.

Concentrate for Solution for Infusion (sterile concentrate)

Clear, colourless liquid.

pH between 7 and 8.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Posology

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

The recommended dosage of PREVYMIS is 480 mg once daily.

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

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

Dosage adjustment

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

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

Missed dose

Patients should be instructed that if they miss a dose of PREVYMIS, they should take it as soon as they remember. If they do not remember until it is time for the next dose, 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 one.

Special populations

Elderly

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

Hepatic impairment

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

Combined hepatic and renal impairment

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

Renal impairment

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

PREVYMIS Concentrate for Solution for Infusion contains hydroxypropylbetadex. The anticipated clinical exposure to hydroxypropylbetadex with intravenously administered letermovir is expected to be approximately 3 600 mg/day for a letermovir dose of 480 mg. There were no cases of kidney injury caused by hydroxypropylbetadex in human studies of

intravenously administered letermovir with treatment durations of up to 47 days. In patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min) receiving PREVYMIS, accumulation of hydroxypropylbetadex could occur (see section 5.3). Serum creatinine levels should be closely monitored in these patients.

Paediatric population

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

No data are available (see section 5.1).

Method of administration

For oral use.

The tablet(s) should be swallowed whole and may be taken with or without food. The tablet(s) should not be divided, crushed or chewed.

For intravenous use only.

PREVYMIS Concentrate for Solution for Infusion requires dilution (see section 6.6) prior to administration.

PREVYMIS diluted solution must be administered through a sterile 0,2 micron or 0,22 micron polyethersulfone (PES) in-line filter. Do not administer the diluted solution through a filter other than a sterile 0,2 micron or 0,22 micron PES in-line filter.

PREVYMIS should be administered as an intravenous (IV) infusion only. PREVYMIS should not be administered as an intravenous push or bolus.

After dilution, PREVYMIS should be administered by intravenous infusion via peripheral or central venous catheter using a total time of approximately 60 minutes. The entire contents of the IV bag should be administered.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Monitoring of CMV DNA

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

Risk of adverse reactions or reduced therapeutic effect due to medicinal product interactions

The concomitant use of PREVYMIS and certain medicinal products may result in known or potentially significant medicinal product interactions, some of which may lead to:

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

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

Medicine interactions

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

Increased monitoring of ciclosporin, tacrolimus, sirolimus is 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 Tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

PREVYMIS 240 mg Concentrate for Solution for Infusion contains 23 mg (or 1,0 mmoL) sodium per dose. This should be taken into consideration by patients on a controlled sodium diet.

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 ciclosporin.
- The combination of ciclosporin 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 PREVYMIS (with or without ciclosporin) with strong and moderate inducers of transporters (e.g. P-gp) and/or enzymes (e.g. UGTs) is not recommended, as it may lead to subtherapeutic letermovir exposure (see **Table 1**).

- Examples of strong inducers include rifampicin, phenytoin, carbamazepine, St John's wort (*Hypericum perforatum*), rifabutin and phenobarbital.
- Examples of moderate inducers include thioridazine, modafinil, ritonavir, lopinavir, efavirenz and etravirine.

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

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

Inhibitors of OATP1B1 or 3

Co-administration of PREVYMIS with medicinal products that are inhibitors of OATP1B1/3 transporters may result in increased letermovir plasma concentrations. If PREVYMIS is co-administered with ciclosporin (a potent OATP1B1/3 inhibitor), the recommended dose of

PREVYMIS is 240 mg once daily (see **Table 1** and sections 4.2 and 5.2). Caution is advised if other

OATP1B1/3 inhibitors are added to letermovir combined with ciclosporin.

- 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 ciclosporin is concomitantly used. The full induction effect can be expected after 10 to 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, amphotericin B and micafungin. The potential interaction between letermovir and these medicinal products have not been investigated. There is a theoretical risk of reduced exposure due to induction, but the size of the effect and thus clinical relevance is presently unknown.

Medicinal products metabolised by CYP3A

Letermovir is a moderate inhibitor of CYP3A *in vivo*. Co-administration of PREVYMIS with oral midazolam (a CYP3A substrate) results in 2- to 3-fold increased midazolam plasma concentrations. Co-administration of PREVYMIS may result in clinically relevant increases in the plasma concentrations of co-administered CYP3A substrates (see sections 4.3, 4.4 and 5.2).

- Examples of such medicinal products include certain immunosuppressants (e.g. ciclosporin, 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 ciclosporin is concomitantly used.

Due to time dependent inhibition and simultaneous induction the net enzyme inhibitory effect may not be reached until after 10 to 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 to 14 days for the inhibitory effect to disappear. If monitoring is applied, this is recommended the first 2 weeks after initiating and ending letermovir (see section 4.4) as well as after changing route of letermovir administration.

Medicinal products transported by OATP1B1/3

Letermovir is an inhibitor of OATP1B1/3 transporters. Administration of PREVYMIS may result in a clinically relevant increase in plasma concentrations of co-administered medicinal products that are OATP1B1/3 substrates.

- Examples of such medicinal products include HMG CoA reductase inhibitors, fexofenadine, repaglinide and glyburide (see **Table 1**). Comparing letermovir regimen administered without ciclosporin, the effect is more marked after IV than oral letermovir.

The magnitude of the OATP1B1/3 inhibition on co-administered medicinal products is likely greater when PREVYMIS is co-administered with ciclosporin (a potent OATP1B1/3 inhibitor). This needs to be considered when the letermovir regimen is changed during treatment with an OATP1B1/3

substrate.

Medicinal products metabolised by CYP2C9 and/or CYP2C19

Co-administration of PREVYMIS with voriconazole (a CYP2C19 substrate) results in significantly decreased voriconazole plasma concentrations, indicating that letermovir is an inducer of CYP2C19.

CYP2C9 is likely also induced. Letermovir has the potential to decrease the exposure of CYP2C9 and/or CYP2C19 substrates potentially resulting in subtherapeutic levels.

- Examples of such medicinal products include warfarin, voriconazole, diazepam, lansoprazole, omeprazole, esomeprazole, pantoprazole, tilidine, tolbutamide (see **Table 1**). The effect is expected to be less pronounced for oral letermovir without ciclosporin, than IV letermovir with or without ciclosporin or oral letermovir with ciclosporin. 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 **Table1**).

Concomitant use of repaglinide and letermovir with or without ciclosporin is not recommended.

Medicinal products transported by P-gp in the intestine

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

Medicinal products metabolised by CYP2B6, UGT1A1 or transported by BCRP or OATP2B1

Letermovir is a general inducer *in viv*o but has also been observed to inhibit CYP2B6, UGT1A1, BCRP and OATP2B1 *in vitro*. The net effect *in vivo* is unknown. Therefore, the

plasma concentrations of medicinal products that are substrates of these enzymes or transporters may increase or decrease

when co-administered with letermovir. Additional monitoring may be recommended; refer to the prescribing information for such medicinal products.

- Examples of medicinal products that are metabolised by CYP2B6 include bupropion.
- Examples of medicinal products metabolised by UGT1A1 are raltegravir and dolutegravir.
- Examples of medicinal products transported by BCRP include rosuvastatin and sulfasalazine.
- An example of 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 cilastatin.

General information

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

Table 1 provides a listing of established or potentially clinically significant medicinal product interactions. The medicinal product interactions described are based on studies conducted

with PREVYMIS or are predicted medicinal product interactions that may occur with PREVYMIS (see sections 4.3, 4.4, 5.1 and 5.2).

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

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

Concomitant medicinal product	**Effect on concentration[†] Mean ratio (90 % confidence interval) for AUC, C_{max} (likely mechanism of action)**	**Recommendations concerning co-administration with PREVYMIS**
Antibiotics		
nafcillin	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	Nafcillin may decrease plasma concentrations of letermovir.

		Co-administration of PREVYMIS 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 (1,02, 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 PREVYMIS and rifabutin is not recommended.
rifampicin		
(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)	Multiple dose rifampicin decreases plasma concentrations of letermovir.

	(OATP1B1/3 and/or P-gp inhibition)	Co-administration of PREVYMIS and rifampicin is not recommended.
(600 mg single dose IV)/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	Thioridazine may decrease plasma concentrations of letermovir.

	(P-gp/UGT induction)	Co-administration of PREVYMIS 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 PREVYMIS 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 PREVYMIS 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 PREVYMIS 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 PREVYMIS 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 PREVYMIS[#]. Although not studied, when PREVYMIS is co-administered with ciclosporin, the magnitude of the increase in atorvastatin plasma concentrations is expected to be greater than with PREVYMIS alone. When PREVYMIS is co-administered with ciclosporin, atorvastatin is contraindicated.
simvastatin, pitavastatin, rosuvastatin	Interaction not studied. Expected: ↑ concentrations of HMG-CoA reductase inhibitors (CYP3A, OATP1B1/3 inhibition)	Letermovir may substantially increase plasma concentrations of these statins. Concomitant use is not recommended with PREVYMIS alone.

		When PREVYMIS is co-administered with ciclosporin, use of these statins is contraindicated.
fluvastatin, pravastatin	Interaction not studied. Expected: ↑ concentrations of HMG-CoA reductase inhibitors (OATP1B1/3 and/or BCRP inhibition)	Letermovir may increase statin plasma concentrations. When PREVYMIS is co-administered with these statins, a statin dose reduction may be necessary[#]. Statin-associated adverse events such as myopathy should be closely monitored. When PREVYMIS is co-administered with ciclosporin, 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		
ciclosporin (50 mg single dose)/letermovir (240 mg daily)	↑ ciclosporin AUC 1,66 (1,51, 1,82) C_{max} 1,08 (0,97, 1,19) (CYP3A inhibition)	If PREVYMIS is co-administered with ciclosporin, the dosage of PREVYMIS should be decreased to 240 mg once daily (see sections 4.2 and 5.1). Frequent monitoring of ciclosporin whole blood concentrations should be performed during treatment, when changing PREVYMIS administration route, and at discontinuation of PREVYMIS and the dose of ciclosporin adjusted accordingly[#].
ciclosporin (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	No dose adjustment required.

	AUC 1,18 (1,04, 1,32) C_{max} 1,11 (0,93, 1,34)	
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 PREVYMIS administration route and at discontinuation of PREVYMIS and the dose of sirolimus adjusted accordingly#. Frequent monitoring of sirolimus concentrations is recommended at initiation or discontinuation of ciclosporin co-administration with PREVYMIS. When PREVYMIS is co-administered with ciclosporin, also refer to the sirolimus prescribing

		information for specific dosing recommendations for use of sirolimus with ciclosporin. When PREVYMIS is co-administered with ciclosporin, the magnitude of the increase in concentrations of sirolimus may be greater than with PREVYMIS alone.
tacrolimus (5 mg single dose)/letermovir (480 mg daily)	↑ tacrolimus 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 PREVYMIS administration route and at discontinuation of PREVYMIS and the dose of tacrolimus adjusted accordingly[#].
tacrolimus (5 mg single dose)/letermovir (80 mg twice daily)	↔ letermovir AUC 1,02 (0,97, 1,07) C_{max} 0,92 (0,84, 1,00)	
Oral contraceptives		
ethinylestradiol (EE) (0,03 mg)/levonorgestrel (LNG)[‡]	↔ EE AUC 1,42 (1,32, 1,52)	No dose adjustment required.

(0,15 mg) single dose/letermovir (480 mg daily)	C_{max} 0,89 (0,83, 0,96) ↔ LNG AUC 1,36 (1,30, 1,43) C_{max} 0,95 (0,86, 1,04)	
Other systemically acting oral contraceptive steroids	Risk of ↓ concentrations 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 ↓ concentrations of repaglinide	Letermovir may increase or decrease the plasma concentrations of repaglinide. (The net effect is not known). Concomitant use is not recommended. When

	(CYP2C8 induction, CYP2C8 and OATP1B inhibition)	PREVYMIS is co-administered with ciclosporin, the plasma concentrations of repaglinide is expected to increase due to the additional OATP1B inhibition by ciclosporin. Concomitant use is not recommended[#].
glyburide	Interaction not studied. Expected: ↑ concentrations of 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 PREVYMIS is co-administered with

		ciclosporin, 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 PREVYMIS 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 PREVYMIS 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 PREVYMIS 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 PREVYMIS is co-administered with ciclosporin, dabigatran is contraindicated.
Sedatives		
midazolam (1 mg single dose IV)/letermovir (240 mg once daily PO) midazolam (2 mg single dose PO)/letermovir (240 mg once daily PO)	↑ midazolam IV: 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 PREVYMIS with midazolam. Dose adjustment of midazolam should be considered[#]. The increase in midazolam plasma concentration may be greater when oral midazolam is administered with letermovir at the clinical dose than with the dose studied.
Opioid agonists		
Examples: alfentanil, fentanyl	Interaction not studied.	Frequent monitoring for adverse reactions related

	Expected: ↑ concentrations of CYP3A metabolised opioids (CYP3A inhibition)	to these medicinal products is recommended during co-administration. Dose adjustment of CYP3A metabolised opioids may be needed[#] (see section 4.4). Monitoring is also recommended if changing route of administration. When PREVYMIS is co-administered with ciclosporin, the magnitude of the increase in plasma concentrations of CYP3A metabolised opioids may be greater. Close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised during co-administration of PREVYMIS in combination with ciclosporin and

		alfentanil or fentanyl. Refer to the respective prescribing information (see section 4.4).
Anti-dysrhythmic medicinal products		
amiodarone	Interaction not studied. Expected: ↑ concentrations of 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 PREVYMIS[#].
quinidine	Interaction not studied. Expected:	Letermovir may increase the plasma concentrations of quinidine.

	↑ concentrations of quinidine (CYP3A inhibition)	Close clinical monitoring should be exercised during administration of PREVYMIS 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)	Letermovir may decrease the plasma concentrations of CYP2C19 substrates. Clinical monitoring and dose adjustment may be needed.
	Interaction not studied. Expected: ↔ letermovir	

pantoprazole	Interaction not studied. Expected: ↓ pantoprazole (likely due to induction of CYP2C19)	Letermovir may decrease the plasma concentrations of CYP2C19 substrates. Clinical monitoring and dose adjustment may be needed.
	Interaction not studied. Expected: ↔ letermovir	
Wakefulness-promoting medicines		
modafinil	Interaction not studied. Expected: ↓ letermovir (P-gp/UGT induction)	Modafinil may decrease plasma concentrations of letermovir. Co-administration of PREVYMIS and modafinil is not recommended.

*This table is not all inclusive.

†↓=decrease, ↑=increase

↔=no clinically relevant change

‡One-way interaction study assessing the effect of letermovir on the concomitant medicinal product.

§These data are the effect of rifampicin on letermovir 24 hours after final rifampicin dose.

#Refer to the respective prescribing information.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of letermovir in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

PREVYMIS is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding

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.

Mothers should not breastfeed their infants while receiving PREVYMIS.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a) Summary of safety profile

The safety assessment of PREVYMIS was based on a Phase 3 clinical trial (P001) in HSCT recipients who received PREVYMIS or placebo through Week 14 post-transplant and were followed for safety through Week 24 post-transplant (see section 5.1).

The most commonly reported adverse reactions occurring in at least 1 % of subjects in the PREVYMIS group and at a frequency greater than placebo were: nausea (7,2 %), diarrhoea (2,4 %) and vomiting (1,9 %).

The most frequently reported adverse reactions that led to discontinuation of PREVYMIS were nausea (1,6 %), vomiting (0,8 %) and abdominal pain (0,5 %).

b) Tabulated summary of adverse reactions

The following adverse reactions were identified in patients taking PREVYMIS in clinical trials. The adverse reactions are listed below by body system organ class and frequency.

Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000) or very rare (< 1/10 000).

Table 2: Adverse reactions identified with PREVYMIS

Frequency	Adverse reactions
Immune system disorders	
Uncommon	hypersensitivity
Metabolism and nutrition disorders	
Uncommon	decreased appetite
Nervous system disorders	
Uncommon	dysgeusia, headache
Ear and labyrinth disorders	

Uncommon	vertigo
Gastrointestinal disorders	
Common	nausea, diarrhoea, vomiting
Uncommon	abdominal pain
Hepatobiliary disorders	
Uncommon	alanine aminotransferase increased, aspartate aminotransferase increased
Musculoskeletal and connective tissue disorders	
Uncommon	muscle spasms
Renal and urinary disorders	
Uncommon	blood creatinine increased
General disorders and administration site conditions	
Uncommon	fatigue, oedema peripheral

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

There is no experience with human overdose with PREVYMIS. During Phase 1 clinical trials, 86 healthy subjects received doses ranging from 720 mg/day to 1 440 mg/day of PREVYMIS for up to 14 days. The adverse reaction profile was similar to that of the clinical dose of 480

mg/day. There is no specific antidote for overdose with PREVYMIS. In case of overdose, it is recommended that the patient be monitored for adverse reactions and appropriate symptomatic treatment instituted.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Letermovir inhibits the CMV DNA terminase complex which is required for cleavage and packaging of viral progeny DNA. Letermovir affects the formation of proper unit length genomes and interferes with virion maturation.

Antiviral activity

The median EC_{50} value of letermovir against a collection of clinical CMV isolates in a cell-culture model of infection was 2,1 nM (range=0,7 nM to 6,1 nM, n=74).

Viral resistance

In cell culture

The CMV genes UL51, UL56 and UL89 encode subunits of CMV DNA terminase. CMV mutants with reduced susceptibility to letermovir have been selected in cell culture and the substitutions map to pUL51 (P91S) pUL56 (C25F, S229F, V231A, V231L, N232Y, V236A,

V236L, V236M, E237D, L241P, T244K, T244R, L254F, L257F, L257I, K258E F261C, F261L, F261S, Y321C, C325F, C325R, C325W, C325Y, L328V, M329T, A365S, N368D, R369G, R369M, R369S) and pUL89 (N320H, D344E). EC_{50} values for recombinant CMV mutants expressing these substitutions are 1,6- to 9 300-fold higher than those for the wild-type reference virus.

In clinical studies

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

In a Phase 3 trial (P001), DNA sequence analysis of the entire coding regions of UL56 and UL89 was performed on samples obtained from 40 letermovir-treated subjects, in the FAS population who experienced prophylaxis failure and for whom samples were available for analysis. A total of 2 letermovir resistance-associated substitutions both mapping to pUL56 were detected in 2 subjects. One subject had the substitution V236M and the other had E237G.

Cross-resistance

Cross-resistance is not likely with medicinal products with a different mechanism of action. Letermovir is fully active against viral populations with substitutions conferring resistance to CMV DNA polymerase inhibitors (ganciclovir, cidofovir and foscarnet). A panel of recombinant CMV strains with substitutions conferring resistance to letermovir was fully

susceptible to cidofovir, foscarnet and ganciclovir with the exception of a recombinant strain with the pUL56 E237G substitution which confers a 2,1-fold reduction in ganciclovir susceptibility relative to wild-type.

Cardiac electrophysiology

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

Paediatric population

Safety and efficacy of letermovir have not been established in patients younger than18 years of age. No data are available.

5.2 Pharmacokinetic properties

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

In healthy subjects, the geometric mean steady-state AUC and C_{max} values were 71 500 ng•hr/mL and 13 000 ng/mL, respectively, with 480 mg once daily oral letermovir. Letermovir reached steady-state in 9 to 10 days with an accumulation ratio of 1,2 for AUC and 1,0 for C_{max}.

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

Table 3: Letermovir AUC (ng•hr/mL) values in HSCT Recipients

Treatment Regimen	Median (90 % Prediction Interval)*
480 mg Oral, no ciclosporin	34 400 (16 900, 73 700)
480 mg IV, no ciclosporin	100 000 (65 300, 148 000)
240 mg Oral, with ciclosporin	60 800 (28 700, 122 000)
240 mg IV, with ciclosporin	70 300 (46 200, 106 000)
*Medians and 90 % prediction intervals are based on simulations using the Phase 3 population PK model with inter-individual variability.	

Absorption: Letermovir was absorbed rapidly with a median time to maximum plasma concentration (T_{max}) of 1,5 to 3 hours and declined in a biphasic manner. In HSCT recipients, bioavailability of letermovir was estimated to be approximately 35 % with 480 mg once daily oral letermovir administered without ciclosporin. The inter-individual variability for bioavailability was estimated to be approximately 37 %.

Effect of ciclosporin: In HSCT recipients, co-administration of ciclosporin increased plasma concentrations of letermovir due to inhibition of OATP1B. Bioavailability of letermovir was estimated to be approximately 85 % with 240 mg once daily oral letermovir co-administered with ciclosporin in patients.

If letermovir is co-administered with ciclosporin, the recommended dose of letermovir is 240 mg once daily (see section 4.2).

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

Distribution: Based on population pharmacokinetic analyses, the mean steady-state volume of distribution is estimated to be 45,5 L following intravenous administration in HSCT recipients.

Letermovir is extensively bound (98,2 %) to human plasma proteins, independent of the concentration range (3 to 100 mg/L) evaluated, *in vitro*. Some saturation was observed at lower concentrations.

Blood to plasma partitioning of letermovir is 0.56 and independent of the concentration range (0,1 to 10 mg/L) evaluated *in vitro*.

In preclinical distribution studies, letermovir is distributed to organs and tissues with the highest concentrations observed in the gastrointestinal tract, bile duct and liver and low concentrations in the brain.

Biotransformation: The majority of letermovir-related components in plasma is unchanged parent (96,6 %). No major metabolites are detected in plasma. Letermovir is partly eliminated by glucuronidation mediated by UGT1A1/1A3.

Elimination: The mean apparent terminal half-life for letermovir is approximately 12 hours with 480 mg IV letermovir in healthy subjects. The major elimination pathways of letermovir is biliary excretion as well as direct glucuronidation. The process involves the hepatic uptake transporters OATP1B1 and 3 followed by UGT1A1/3 catalysed glucuronidation.
Based on population pharmacokinetic analyses, letermovir steady-state apparent CL is estimated to be 4,84 L/hr following intravenous administration of 480 mg in HSCT recipients. The inter-individual variability for CL is estimated to be 24,6 %.

Excretion: After oral administration of radio-labelled letermovir, 93,3 % of radioactivity was recovered in faeces. The majority of letermovir was biliary excreted as unchanged parent with a minor amount (6 % of dose) as an acyl-glucuronide metabolite in faeces. The acyl-glucuronide is unstable in faeces. Urinary excretion of letermovir was negligible (< 2 % of dose).

Pharmacokinetics in special populations

Hepatic impairment

Letermovir unbound AUC was approximately 81 % and 4-fold higher in subjects with moderate (Child-Pugh Class B [CP-B], score of 7 to 9) and severe (Child-Pugh Class C [CP-C], score of 10 to 15) hepatic impairment, respectively, compared to healthy subjects. The changes in letermovir exposure in subjects with moderate hepatic impairment are not clinically relevant.
Marked increases in letermovir unbound exposure are anticipated in patients with moderate hepatic impairment combined with moderate or severe renal impairment (see section 4.2).

Renal impairment

Letermovir unbound AUC was approximately 115 and 81 % higher in subjects with moderate (eGFR of 31,0 to 56,8 mL/min/1,73m^2) and severe (eGFR of 11,9 to 28,1 mL/min/1,73m^2) renal impairment, respectively, compared to healthy subjects. The changes in letermovir exposure due to moderate or severe renal impairment are not considered to be clinically relevant. Subjects with ESRD have not been studied.

Weight

Based on population pharmacokinetic analyses, letermovir AUC is estimated to be 18,7 % lower in subjects weighing 80 to 100 kg compared to subjects weighing 67 kg. This difference is not clinically relevant.

Race

Based on population pharmacokinetic analyses, letermovir AUC is estimated to be 33,2 % higher in Asians compared to Whites. This change is not clinically relevant.

Gender

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

Elderly

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

5.3 Preclinical safety data

General toxicity

Irreversible testicular toxicity was noted only in rats at systemic exposures (AUC) ≥ 3-fold the exposures in humans at the recommended human dose (RHD). This toxicity was 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 IV letermovir formulated with 1 500 mg/kg/day of the cyclodextrin excipient hydroxypropylbetadex.

Carcinogenesis

Carcinogenicity studies with letermovir have not been conducted.

Mutagenesis

Letermovir was not genotoxic in a battery of *in vitro* or *in vivo* assays, including microbial mutagenesis assays, chromosomal aberration in Chinese Hamster Ovary cells and in an *in vivo* mouse micronucleus study.

Reproduction

Fertility

In the fertility and early embryonic development studies in the rat, there were no effects of letermovir on female fertility. In male rats, reduced sperm concentration, reduced sperm

motility and decreased fertility were observed at systemic exposures ≥ 3-fold the AUC in humans at the RHD (see General toxicity).

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

Development

In rats, maternal toxicity (including decrease in body weight gain) was noted at 250 mg/kg/day (approximately 11-fold the AUC at the RHD); in the offspring, decreased foetal weight with delayed ossification, slightly oedematous foetuses, and increased incidence of shortened umbilical cords and of variations and malformations in the vertebrae, ribs, and pelvis were observed. No maternal or developmental effects were noted at the dose of 50 mg/kg/day (approximately 2,5-fold the AUC at the RHD).

In rabbits, maternal toxicity (including mortality and abortions) was noted at 225 mg/kg/day (approximately 2-fold the AUC at the RHD); in the offspring, an increased incidence of malformations and variations in the vertebrae and ribs were observed.

In the pre- and post-natal developmental study, letermovir was administered orally to pregnant rats. There was no developmental toxicity observed up to the highest exposure tested (2-fold the AUC at the RHD).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

PREVYMIS 240 mg Film-coated Tablets

Tablet core: microcrystalline cellulose (E460); croscarmellose sodium (E468); povidone (E1201); colloidal anhydrous silica (E551) and magnesium stearate (E470b).

Film-coating: lactose monohydrate; hypromellose (E464); titanium dioxide (E171); triacetin (E1518); iron oxide yellow (E172) and carnauba wax (E903).

PREVYMIS 240 mg Concentrate for Solution for Infusion

Hydroxypropylbetadex (cyclodextrin); sodium chloride; sodium hydroxide (E524) and water for injections.

6.2 Incompatibilities

PREVYMIS 240 mg Film-coated Tablets

Not applicable.

PREVYMIS 240 mg Concentrate for Solution for Infusion

Incompatible medicinal products

PREVYMIS Concentrate for Solution for Infusion is physically incompatible with amiodarone hydrochloride, amphotericin B (liposomal), aztreonam, cefepime hydrochloride, ciprofloxacin, ciclosporin, 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) plasticisers and polyurethane-containing IV administration set tubing.

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

6.3 Shelf life

PREVYMIS 240 mg Film-coated Tablets

36 months

PREVYMIS 240 mg Concentrate for Solution for Infusion

Unopened vial: 36 months

After opening: Use immediately

Storage of diluted solution

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

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

6.4 Special precautions for storage

PREVYMIS 240 mg Film-coated Tablets

Store at or below 30 °C. Store in the original package in order to protect from moisture.

PREVYMIS 240 mg Concentrate for Solution for Infusion

Store at or below 25 °C. 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

PREVYMIS 240 mg Film-coated Tablets

Polyamide/Aluminium/PVC – Aluminium blister card. Each carton contains four (4) 7-count blister cards for a total of 28 tablets.

PREVYMIS 240 mg Concentrate for Solution for Infusion

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) of solution.

Pack size: 1 vial.

6.6 Special precautions for disposal and other handling

PREVYMIS 240 mg Film-coated Tablets

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

PREVYMIS 240 mg Concentrate for Solution for Infusion

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 liquid and may contain a few product-related small translucent or white particles.

Do not use the vial if the solution is cloudy, discoloured or contains matter other than a few small translucent or white particles.

Do not use PREVYMIS Concentrate for Solution for Infusion with IV bags and infusion set materials containing polyurethane or the plasticiser diethylhexyl phthalate (DEHP). Materials that are phthalate-free are also DEHP-free.

Do not shake PREVYMIS vial.

Add one single-dose vial (12 mL [240 mg dose]) or two single-dose vials (2 x 12 mL [480 mg dose]) of PREVYMIS Concentrate for Solution for Infusion to a 250 mL pre-filled IV bag containing either 0,9 % sodium chloride or 5 % dextrose and mix the diluted solution by gentle inversion. Do not shake.

Once diluted, the solution of PREVYMIS is clear and ranges from colourless to yellow. Variations of colour within this range do not affect the quality of the product. The diluted solution should be inspected visually for particulate matter and discolouration prior to administration. Discard if the diluted solution is cloudy, discoloured or contains matter other than a few small translucent or white particles. If one vial is added to a 250 mL IV diluent bag, the final concentration of letermovir would be 0,9 mg/mL (for 240 mg dose). If two vials are added to a 250 mL IV diluent bag, the final concentration of letermovir would be 1,8 mg/mL (for 480 mg dose).

Administration

See section 4.2.

PREVYMIS diluted solution must be administered through a sterile 0,2 micron or 0,22 micron polyethersulfone (PES) in-line filter.

Compatible intravenous solutions and other medicinal products

PREVYMIS Concentrate for Solution for Infusion is compatible with 0,9 % sodium chloride and 5 % dextrose solutions.

PREVYMIS Concentrate for Solution for Infusion 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 sulphate
- 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 sulphate
- 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 Concentrate for Solution for Infusion 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).

Plasticisers

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 HOLDER OF CERTIFICATE OF REGISTRATION

MSD (Pty) Ltd, 117 16th Road, Halfway House 1685, South Africa

8 REGISTRATION NUMBERS

PREVYMIS Film-coated Tablets: 54/20.2.8/0429

PREVYMIS Concentrate for Solution for Infusion: 54/20.2.8/0428

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 November 2022

10 DATE OF REVISION OF THE TEXT