## 1. NAME OF THE MEDICINAL PRODUCT

PREVYMIS 20 mg granules
PREVYMIS 120 mg granules

## 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).

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 .

Posology

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

Letermovir tablets and granules in sachet may be used interchangeably at the discretion of the physician.

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 |

*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 have not been established. No data are available.

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).

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 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 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 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).

*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).
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 cyclosporine is discontinued during letermovir 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 oral letermovir with cyclosporine. This needs to be considered when cyclosporine is discontinued during letermovir 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 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 cyclosporine is concomitantly used. When 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.<br>Expected:<br>↓ letermovir<br><br>(P-gp/UGT induction) | Nafcillin may decrease plasma concentrations of letermovir.<br>Co-administration of letermovir and nafcillin is not recommended. |
| **Antifungals** | | |
| fluconazole (400 mg single dose)/letermovir (480 mg single dose) | ↔ fluconazole<br>AUC 1.03 (0.99, 1.08)<br>$C_{max}$ 0.95 (0.92, 0.99)<br>↔ letermovir<br>AUC 1.11 (1.01, 1.23)<br>$C_{max}$ 1.06 (0.93, 1.21)<br><br>Interaction at steady state not studied.<br>Expected:<br>↔ fluconazole<br>↔ letermovir | No dose adjustment required. |
| itraconazole (200 mg once daily PO)/letermovir (480 mg once daily PO) | ↔ itraconazole<br>AUC 0.76 (0.71, 0.81)<br>$C_{max}$ 0.84 (0.76, 0.92)<br><br>↔ letermovir<br>AUC 1.33 (1.17, 1.51)<br>$C_{max}$ 1.21 (1.05, 1.39) | No dose adjustment required. |

| **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** |
|---|---|---|
| posaconazole[‡] (300 mg single dose)/ letermovir (480 mg daily) | ↔ posaconazole<br>AUC 0.98 (0.82, 1.17)<br>$C_{max}$ 1.11 (0.95, 1.29) | No dose adjustment required. |
| voriconazole[‡] (200 mg twice daily)/ letermovir (480 mg daily) | ↓ voriconazole<br>AUC 0.56 (0.51, 0.62)<br>$C_{max}$ 0.61 (0.53, 0.71)<br><br>(CYP2C9/19 induction) | If concomitant administration is necessary, TDM for voriconazole is recommended the first 2 weeks after initiating or ending letermovir, as well as after changing immunosuppressant. |
| **Antimycobacterials** | | |
| rifabutin | Interaction not studied.<br>Expected:<br>↓ letermovir<br><br>(P-gp/UGT induction) | Rifabutin may decrease plasma concentrations of letermovir.<br>Co-administration of letermovir and rifabutin is not recommended. |
| rifampicin | | Multiple dose rifampicin decreases plasma concentrations of letermovir.<br>Co-administration of letermovir and rifampicin is not recommended. |
| (600 mg single dose PO)/ letermovir (480 mg single dose PO) | ↔letermovir<br>AUC 2.03 (1.84, 2.26)<br>$C_{max}$ 1.59 (1.46, 1.74)<br>$C_{24}$ 2.01 (1.59, 2.54)<br><br>(OATP1B1/3 and/or P-gp inhibition) | |
| (600 mg single dose intravenous)/ letermovir (480 mg single dose PO) | ↔ letermovir<br>AUC 1.58 (1.38, 1.81)<br>$C_{max}$ 1.37 (1.16, 1.61)<br>$C_{24}$ 0.78 (0.65, 0.93)<br><br>(OATP1B1/3 and/or P-gp inhibition) | |
| (600 mg once daily PO)/ letermovir (480 mg once daily PO) | ↓ letermovir<br>AUC 0.81 (0.67, 0.98)<br>$C_{max}$ 1.01 (0.79, 1.28)<br>$C_{24}$ 0.14 (0.11, 0.19)<br><br>(Sum of OATP1B1/3 and/or P-gp inhibition and P-gp/UGT induction) | |
| (600 mg once daily PO (24 hours after rifampicin))[§]/ letermovir (480 mg once daily PO) | ↓ letermovir<br>AUC 0.15 (0.13, 0.17)<br>$C_{max}$ 0.27 (0.22, 0.31)<br>$C_{24}$ 0.09 (0.06, 0.12)<br><br>(P-gp/UGT induction) | |
| **Antipsychotics** | | |
| thioridazine | Interaction not studied.<br>Expected:<br>↓ letermovir<br><br>(P-gp/UGT induction) | Thioridazine may decrease plasma concentrations of letermovir.<br>Co-administration of letermovir and thioridazine is not recommended. |
| **Endothelin antagonists** | | |

| **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** |
|---|---|---|
| bosentan | Interaction not studied.<br>Expected:<br>↓ letermovir<br><br>(P-gp/UGT induction) | Bosentan may decrease plasma concentrations of letermovir.<br>Co-administration of letermovir and bosentan is not recommended. |
| **Antivirals** | | |
| acyclovir[‡]<br>(400 mg single dose)/ letermovir (480 mg daily) | ↔ acyclovir<br>AUC 1.02 (0.87, 1.2)<br>$C_{max}$ 0.82 (0.71, 0.93) | No dose adjustment required. |
| valacyclovir | Interaction not studied.<br>Expected:<br>↔ valacyclovir | No dose adjustment required. |
| **Herbal products** | | |
| St. John's wort (*Hypericum perforatum*) | Interaction not studied.<br>Expected:<br>↓ letermovir<br><br>(P-gp/UGT induction) | St. John's wort may decrease plasma concentrations of letermovir.<br>Co-administration of letermovir and St. John's wort is contraindicated. |
| **HIV medicinal products** | | |
| efavirenz | Interaction not studied.<br>Expected:<br>↓ letermovir<br>(P-gp/UGT induction)<br><br>↑ or ↓ efavirenz<br>(CYP2B6 inhibition or induction) | Efavirenz may decrease plasma concentrations of letermovir.<br>Co-administration of letermovir and efavirenz is not recommended. |
| etravirine, nevirapine, ritonavir, lopinavir | Interaction not studied.<br>Expected:<br>↓ letermovir<br><br>(P-gp/UGT induction) | These antivirals may decrease plasma concentrations of letermovir.<br>Co-administration of letermovir with these antivirals 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 |
|---|---|---|
| **HMG-CoA reductase inhibitors** | | |
| atorvastatin‡ (20 mg single dose)/ letermovir (480 mg daily) | ↑ atorvastatin<br>AUC 3.29 (2.84, 3.82)<br>$C_{max}$ 2.17 (1.76, 2.67)<br><br>(CYP3A, OATP1B1/3 inhibition) | Statin-associated adverse events such as myopathy should be closely monitored. The dose of atorvastatin should not exceed 20 mg daily when co-administered with letermovir#.<br><br>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.<br>Expected:<br>↑ HMG-CoA reductase inhibitors<br><br>(CYP3A, OATP1B1/3 inhibition) | Letermovir may substantially increase plasma concentrations of these statins. Concomitant use is not recommended with letermovir alone.<br><br>When letermovir is co-administered with cyclosporine, use of these statins is contraindicated. |
| fluvastatin, pravastatin | Interaction not studied.<br>Expected:<br>↑ HMG-CoA reductase inhibitors<br><br>(OATP1B1/3 and/or BCRP inhibition) | Letermovir may increase statin plasma concentrations.<br><br>When 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.<br><br>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<br>AUC 1.66 (1.51, 1.82)<br>$C_{max}$ 1.08 (0.97, 1.19)<br>(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).<br><br>Frequent monitoring of cyclosporine whole blood concentrations should be performed during treatment, and at discontinuation of letermovir and the dose of cyclosporine adjusted accordingly[#]. |
| cyclosporine (200 mg single dose)/ letermovir (240 mg daily) | ↑ letermovir<br>AUC 2.11 (1.97, 2.26)<br>$C_{max}$ 1.48 (1.33, 1.65)<br><br>(OATP1B1/3 inhibition) | |
| mycophenolate mofetil (1 g single dose)/ letermovir (480 mg daily) | ↔mycophenolic acid<br>AUC 1.08 (0.97, 1.20)<br>$C_{max}$ 0.96 (0.82, 1.12)<br><br>↔ letermovir<br>AUC 1.18 (1.04, 1.32)<br>$C_{max}$ 1.11 (0.92, 1.34) | No dose adjustment required. |
| sirolimus[‡] (2 mg single dose)/ letermovir (480 mg daily) | ↑ sirolimus<br>AUC 3.40 (3.01, 3.85)<br>$C_{max}$ 2.76 (2.48, 3.06)<br><br>(CYP3A inhibition)<br><br>Interaction not studied.<br>Expected:<br>↔ letermovir | Frequent monitoring of sirolimus whole blood concentrations should be performed during treatment, and at discontinuation of letermovir and the dose of sirolimus adjusted accordingly[#].<br>Frequent monitoring of sirolimus concentrations is recommended at initiation or discontinuation of cyclosporine co-administration with letermovir.<br><br>When letermovir is co-administered with cyclosporine, also refer to the sirolimus prescribing information for specific dosing recommendations for use of sirolimus with cyclosporine.<br><br>When 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<br>AUC 2.42 (2.04, 2.88)<br>$C_{max}$ 1.57 (1.32, 1.86)<br>(CYP3A inhibition) | Frequent monitoring of tacrolimus whole blood concentrations should be performed during treatment, and at discontinuation of letermovir and the dose of tacrolimus adjusted accordingly[#]. |
| tacrolimus (5 mg single dose)/ letermovir (80 mg twice daily) | ↔ letermovir<br>AUC 1.02 (0.97, 1.07)<br>$C_{max}$ 0.92 (0.84, 1.00) | |

| 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 contraceptives** | | |
| ethinylestradiol (EE) (0.03 mg)/ levonorgestrel (LNG)[‡] (0.15 mg) single dose/ letermovir (480 mg daily) | ↔ EE<br>AUC 1.42 (1.32, 1.52)<br>$C_{max}$ 0.89 (0.83, 0.96)<br><br>↔ LNG<br>AUC 1.36 (1.30, 1.43)<br>$C_{max}$ 0.95 (0.86, 1.04) | No dose adjustment required. |
| Other systemically acting oral contraceptive steroids | Risk of ↓ contraceptive steroids | Letermovir may reduce plasma concentrations of other oral contraceptive steroids thereby affecting their efficacy. 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.<br>Expected:<br>↑ or ↓ repaglinide<br><br>(CYP2C8 induction, CYP2C8 and OATP1B inhibition) | Letermovir may increase or decrease the plasma concentrations of repaglinide. (The net effect is not known).<br><br>Concomitant use is not recommended.<br><br>When 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.<br>Expected:<br>↑ glyburide<br><br>(OATP1B1/3 inhibition CYP3A inhibition, CYP2C9 induction) | Letermovir may increase the plasma concentrations of glyburide.<br><br>Frequent monitoring of glucose concentrations is recommended the first 2 weeks after initiating or ending letermovir.<br><br>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.<br>Expected:<br>↓ letermovir<br><br>(P-gp/UGT induction) | Carbamazepine or phenobarbital may decrease plasma concentrations of letermovir.<br>Co-administration of letermovir and carbamazepine or phenobarbital is not recommended. |
| phenytoin | Interaction not studied.<br>Expected:<br>↓ letermovir<br><br>(P-gp/UGT induction)<br><br>↓ phenytoin<br><br>(CYP2C9/19 induction) | Phenytoin may decrease plasma concentrations of letermovir.<br><br>Letermovir may decrease the plasma concentrations of phenytoin.<br><br>Co-administration of letermovir and phenytoin is not recommended. |
| **Oral anticoagulants** | | |
| warfarin | Interaction not studied.<br>Expected:<br>↓ warfarin<br><br>(CYP2C9 induction) | Letermovir may decrease the plasma concentrations of warfarin.<br><br>Frequent monitoring of International Normalised Ratio (INR) should be performed when warfarin is co-administered with letermovir treatment[#]. Monitoring is recommended the first 2 weeks after initiating or ending letermovir, as well as after changing immunosuppressant. |
| dabigatran | Interaction not studied.<br>Expected:<br>↓ dabigatran<br><br>(intestinal P-gp induction) | Letermovir may decrease the plasma concentrations of dabigatran and may decrease efficacy of dabigatran. Concomitant use of dabigatran should be avoided due to the risk of reduced dabigatran efficacy.<br><br>When letermovir is co-administered with cyclosporine, dabigatran is contraindicated. |
| **Sedatives** | | |
| midazolam (1 mg single dose intravenous)/ letermovir (240 mg once daily PO)<br><br>midazolam (2 mg single dose PO) / letermovir (240 mg once daily PO) | ↑ midazolam<br>Intravenous:<br>AUC 1.47 (1.37, 1.58)<br>$C_{max}$ 1.05 (0.94, 1.17)<br><br>PO :<br>AUC 2.25 (2.04, 2.48)<br>$C_{max}$ 1.72 (1.55, 1.92)<br><br>(CYP3A inhibition) | Close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised during co-administration of 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.<br>Expected:<br>↑ CYP3A metabolised opioids<br><br>(CYP3A inhibition) | Frequent monitoring for adverse reactions related to these medicinal products is recommended during co-administration. Dose adjustment of CYP3A metabolised opioids may be needed# (see section 4.4). 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.<br>Expected:<br>↑ amiodarone<br><br>(primarily CYP3A inhibition and CYP2C8 inhibition or induction) | Letermovir may increase the plasma concentrations of amiodarone.<br><br>Frequent monitoring for adverse reactions related to amiodarone is recommended during co-administration. Monitoring of amiodarone concentrations should be performed regularly when amiodarone is co-administered with letermovir#. |
| quinidine | Interaction not studied.<br>Expected:<br>↑ quinidine<br><br>(CYP3A inhibition) | Letermovir may increase the plasma concentrations of quinidine.<br><br>Close clinical monitoring should be exercised during administration of letermovir with quinidine. Refer to the respective prescribing information#. |
| **Cardiovascular medicinal products** | | |
| digoxin‡ (0.5 mg single dose)/ letermovir (240 mg twice daily) | ↔ digoxin<br>AUC 0.88 (0.80, 0.96)<br>$C_{max}$ 0.75 (0.63, 0.89)<br><br>(P-gp induction) | No dose adjustment required. |

| 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.<br>Expected:<br>↓omeprazole<br><br>(induction of CYP2C19)<br><br>Interaction not studied.<br>Expected:<br>↔ letermovir | Letermovir may decrease the plasma concentrations of CYP2C19 substrates.<br><br>Clinical monitoring and dose adjustment may be needed. |
| pantoprazole | Interaction not studied.<br>Expected:<br>↓ pantoprazole<br><br>(likely due to induction of CYP2C19)<br><br>Interaction not studied.<br>Expected:<br>↔ letermovir | Letermovir may decrease the plasma concentrations of CYP2C19 substrates.<br><br>Clinical monitoring and dose adjustment may be needed. |
| **Wakefulness-promoting agents** | | |
| modafinil | Interaction not studied.<br>Expected:<br>↓ letermovir<br><br>(P-gp/UGT induction) | Modafinil may decrease plasma concentrations of letermovir.<br>Co-administration of letermovir and modafinil is not recommended. |
| * This table is not all inclusive.<br>† ↓ =decrease, ↑ =increase<br>↔ =no clinically relevant change<br>‡ One-way interaction study assessing the effect of letermovir on the concomitant medicinal product.<br>§ These data are the effect of rifampicin on letermovir 24 hours after final rifampicin dose.<br># 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 two Phase 3 clinical trials.

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.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

## 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 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).

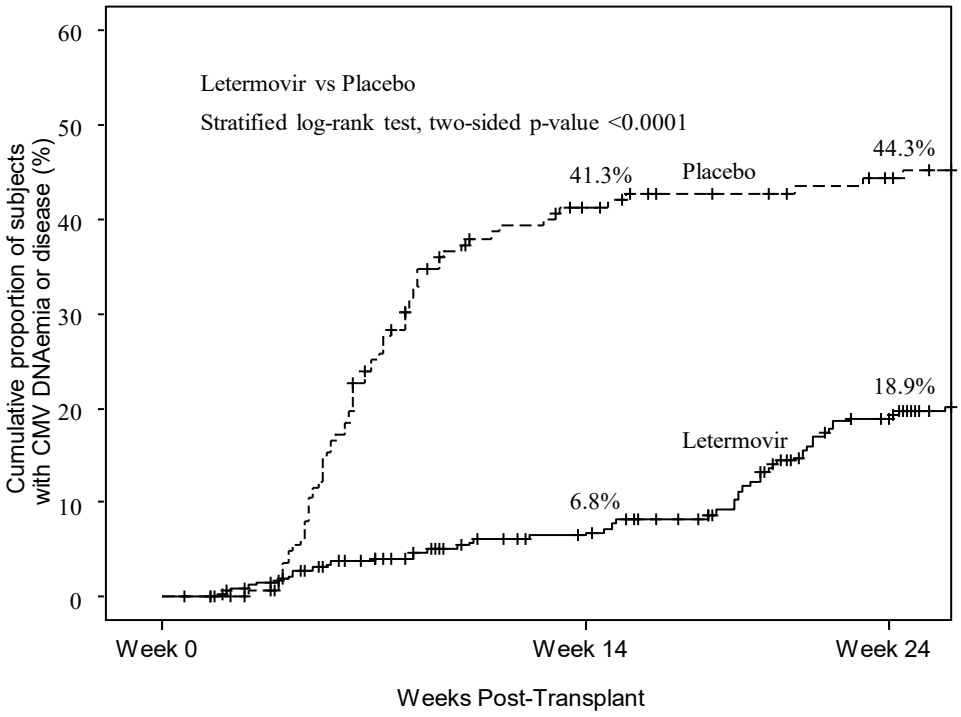
**Table 4: P001: Efficacy results in HSCT recipients (NC=F Approach, FAS Population)**

| **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)**

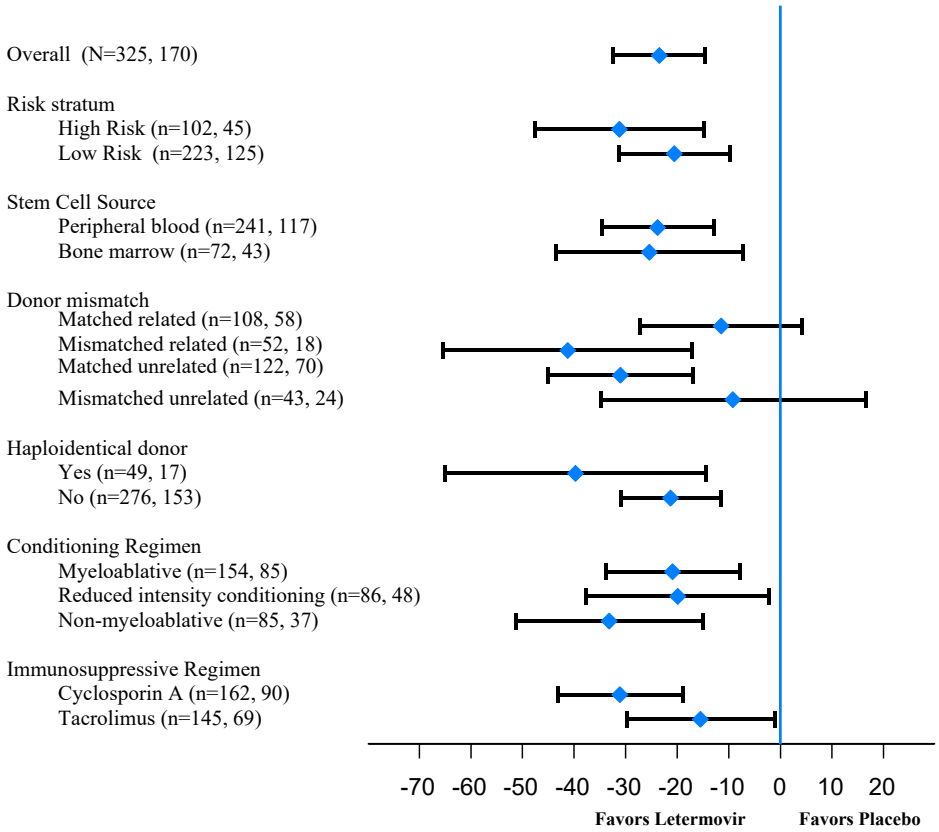



| Number of Subjects at Risk | | | |
|---|---|---|---|
| Letermovir | 325 | 270 | 212 |
| Placebo | 170 | 85 | 70 |

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.

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 administration. Letermovir exposure increased in a greater than dose-proportional manner. The mechanism is likely saturation/autoinhibition of OATP1B1/3. The pharmacokinetics of letermovir have also been characterised following oral administration in adult HSCT recipients (see Table 6) and paediatric HSCT 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 7). 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) |
| 240 mg Oral, with cyclosporine | 60,800 (28,700, 122,000) |
| * Population post-hoc predictions from the population PK analysis using Phase 3 data | |

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%.

*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.

*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. This difference is 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 7). 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 7: 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. | | | | |

## 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
Hypromellose
Croscarmellose sodium
Titanium dioxide
Povidone K-29/32
Lactose monohydrate
Silica, Colloidal Anhydrous
Magnesium stearate
Triacetin
Iron oxide yellow
Iron oxide red

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. It is recommended to store the product at room temperature.

### 6.5 Nature and contents of container

Child-resistant 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** in the product package 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 8 (NG tube) and Table 9 (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 8: 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 9: 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<br><br>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 (Israel-1996) Company Ltd., 34 Ha'charash St., Hod-Hasharon.

## 8. MARKETING AUTHORISATION NUMBER(S)

PREVYMIS 20 mg granules 180-86-38441
PREVYMIS 120 mg granules 180-87-38442

Approved in January 2026.