DOSING AND ADMINISTRATION

PREVYMIS®
(letermovir)
240 mg, 480 mg tablets
Injection 20 mg/mL
Oral pellets 20 mg, 120 mg per packet

Indications

PREVYMIS is indicated for prophylaxis of cytomegalovirus (CMV) infection and disease in adult and pediatric patients 6 months of age and older and weighing at least 6 kg who are CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT).

PREVYMIS is indicated for prophylaxis of CMV disease in adult and pediatric patients 12 years of age and older and weighing at least 40 kg who are kidney transplant recipients at high risk (Donor CMV seropositive/Recipient CMV seronegative [D+/R-]).

Selected Safety Information

PREVYMIS is contraindicated in patients receiving pimozide or ergot alkaloids.

- Increased pimozide concentrations may lead to QT prolongation and torsades de pointes.
- Increased ergot alkaloids concentrations may lead to ergotism.

PREVYMIS is contraindicated with pitavastatin and simvastatin when co-administered with cyclosporine. Significantly increased pitavastatin or simvastatin concentrations may lead to myopathy or rhabdomyolysis.

Selected Safety Information continues on next page.

PREVYMIS is available in 3 formulations

Tablets

- Administer orally with or without food
- Swallow tablets whole

Oral pellets

- Administer orally mixed with soft food or via NG tube or G tube mixed with water
- Do not crush or chew
- **Instructions for Use** should be followed for preparation and administration of PREVYMIS oral pellets

Injection

- PREVYMIS injection must be diluted prior to administration
- The diluted solution is stable for up to 24 hours at room temperature or up to 48 hours under refrigeration
- Administer PREVYMIS through a sterile 0.2 micron or 0.22 micron PES in-line filter
- Administer by IV infusion via a peripheral catheter or central venous line at a constant rate over 1 hour; do not administer as an IV bolus injection
- PREVYMIS injection, which contains hydroxypropyl betadex, should be used only in patients unable to take oral therapy. Patients should be switched to oral PREVYMIS as soon as they are able to take oral medications. If possible, IV administration should not exceed 4 weeks
- Refer to **Prescribing Information** for preparation and administration of IV solution

No dosage adjustment is necessary when switching formulations in adult and pediatric patients 12 years of age and older, and HSCT: weighing at least 30 kg or Kidney Transplant: weighing at least 40 kg.

Dosage adjustment may be necessary for HSCT pediatric patients less than 12 years of age when switching between oral and IV formulations.

For use in patients with renal impairment, refer to the Prescribing Information.

Selected Safety Information (*continued*)

The concomitant use of PREVYMIS and certain drugs may result in potentially significant drug interactions, some of which may lead to adverse reactions (PREVYMIS or concomitant drugs) or reduced therapeutic effect of PREVYMIS or the concomitant drug.

Intravenous formulation of PREVYMIS contains the excipient hydroxypropyl betadex. PREVYMIS injection should be used only in patients unable to take oral therapy and patients should be switched to oral PREVYMIS as soon as they are able to take oral medications. If possible, intravenous administration should not exceed 4 weeks.

Dosage forms and strengths of PREVYMIS

Dosage formulation selection may be dependent upon ability to swallow tablets, age, and weight.

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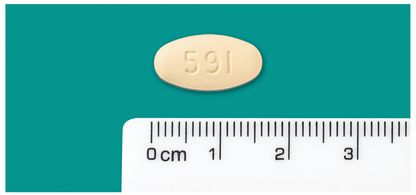
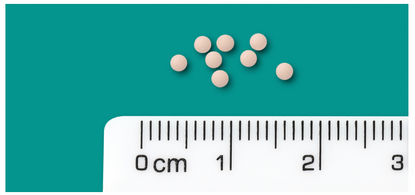
Tablets



240 mg tablet.

480 mg tablet.

Oral Pellets



Contents of a 20-mg packet.

Contents of a 120-mg packet.

Tablets and oral pellets shown as actual size.

Injection

20 mg/mL injection: clear, colorless solution in single-dose vial:

- 240 mg/12 mL vial
- 480 mg/24 mL vial

Selected Safety Information (*continued*)

In patients with renal impairment, accumulation of hydroxypropyl betadex may occur. In adult patients with CLcr less than 50 mL/min and in pediatric patients with a similar degree of renal impairment (based on age-appropriate assessment of renal function) receiving PREVYMIS injection, closely monitor serum creatinine levels.

Animal studies have shown the potential for hydroxypropyl betadex to cause ototoxicity. The active ingredient, letermovir, is not known to be associated with ototoxicity.

Selected Safety Information continues on next page.

G, gastric; IV, intravenous; NG, nasogastric; PES, polyethersulfone.

Recommended dosage

HSCT: adult and pediatric patients 12 years of age and older and weighing at least 30 kg

- The recommended dosage of PREVYMIS is **480 mg** administered orally or intravenously once daily
  - When PREVYMIS is administered orally, the recommended dosage is one 480 mg tablet once daily or two 240 mg tablets once daily
  - Four 120 mg packets of oral pellets once daily can be used for patients who cannot swallow tablets
- Initiate PREVYMIS between Day 0 and Day 28 post-HSCT (before or after engraftment) and continue through Day 100 post-HSCT
- In patients at risk for late CMV infection and disease, PREVYMIS may be continued through Day 200 post-HSCT

Following the completion of PREVYMIS prophylaxis, monitoring for CMV reactivation in HSCT recipients is recommended.

Kidney transplant: adult and pediatric patients 12 years of age and older and weighing at least 40 kg

- The recommended dosage of PREVYMIS is **480 mg** administered orally or intravenously once daily
  - When PREVYMIS is administered orally, the recommended dosage is one 480 mg tablet once daily or two 240 mg tablets once daily
  - Four 120 mg packets of oral pellets once daily can be used for patients who cannot swallow tablets
- Initiate PREVYMIS between Day 0 and Day 7 post-transplant and continue through Day 200 post-transplant

Oral pellets: **Instructions for Use** should be followed for preparation and administration of PREVYMIS oral pellets.

IV: Refer to **Prescribing Information** for IV preparation and administration dosing instructions.

Selected Safety Information (*continued*)

The rate of adverse events occurring in at least 10% of adult HSCT recipients treated with PREVYMIS and at a frequency at least 2% greater than placebo were nausea (27% vs 23%), diarrhea (26% vs 24%), vomiting (19% vs 14%), peripheral edema (14% vs 9%), cough (14% vs 10%), headache (14% vs 9%), fatigue (13% vs 11%), and abdominal pain (12% vs 9%).

Hypersensitivity reaction, with associated moderate dyspnea, occurred in one adult HSCT recipient following the first infusion of IV PREVYMIS after switching from oral PREVYMIS, leading to treatment discontinuation.

Dosage adjustment when co-administered with cyclosporine

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- If oral or IV PREVYMIS is co-administered with cyclosporine, the dosage of PREVYMIS should **be decreased to 240 mg once daily in the following populations:**
  - HSCT: adult and pediatric patients **12 years of age and older** and weighing at least **30 kg**
  - Kidney transplant: adult and pediatric patients **12 years of age and older** and weighing at least **40 kg**
- If cyclosporine is initiated after starting PREVYMIS, the next dose of PREVYMIS should be decreased to 240 mg once daily
- If cyclosporine is discontinued after starting PREVYMIS, the next dose of PREVYMIS should be increased to 480 mg once daily
- If cyclosporine dosing is interrupted due to high cyclosporine levels, no dose adjustment of PREVYMIS is needed

Selected Safety Information (*continued*)

The most common adverse event occurring in at least 10% of adult kidney transplant recipients treated with PREVYMIS and at a frequency greater than valganciclovir was diarrhea (32% vs 29%).

The safety profile of PREVYMIS in pediatric subjects was consistent with the safety profile observed in clinical trials of PREVYMIS in adults.

If PREVYMIS is co-administered with cyclosporine, the dosage of PREVYMIS should be decreased to 240 mg once daily.

If PREVYMIS is co-administered with cyclosporine in pediatric HSCT patients less than 12 years of age, dose adjustment may be required.

Co-administration of PREVYMIS may alter the plasma concentrations of other drugs and other drugs may alter the plasma concentrations of PREVYMIS. Consult the full Prescribing Information prior to and during treatment for potential drug interactions.

Selected Safety Information continues on next page.

CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplant; IV, intravenous.

HSCT: Recommended dosage for pediatric patients 6 months to less than 12 years of age or 12 years of age and older and weighing less than 30 kg

- The recommended dosages of PREVYMIS for pediatric HSCT recipients 6 months to less than 12 years of age are based on weight (see **Table 1** and **Table 2**)
- PREVYMIS can be administered orally (tablet or pellet) or intravenously once daily
- Dosage adjustment may be necessary for pediatric patients less than 12 years of age when switching between oral and IV formulations (see **Table 1** and **Table 2**)
- Initiate PREVYMIS between Day 0 and Day 28 post-HSCT (before or after engraftment) and continue through Day 100 post-HSCT
- In patients at risk for late CMV infection and disease, PREVYMIS may be continued through Day 200 post-HSCT

Following the completion of PREVYMIS prophylaxis, monitoring for CMV reactivation in HSCT recipients is recommended.

Selected Safety Information (*continued*)

Closely monitor serum creatinine levels in patients with CLcr less than 50 mL/min using PREVYMIS injection.

PREVYMIS is not recommended for patients with severe (Child-Pugh Class C) hepatic impairment.

The safety and effectiveness of PREVYMIS have not been established for:

- HSCT recipients less than 6 months of age or weighing less than 6 kg, or
- Kidney transplant recipients less than 12 years of age or weighing less than 40 kg.

For patients with creatinine clearance (CLcr) greater than 10 mL/min (by Cockcroft-Gault equation), no dosage adjustment of PREVYMIS is required based on renal impairment. The safety of PREVYMIS in patients with end-stage renal disease (CLcr less than 10 mL/min), including patients on dialysis, is unknown.

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Table 1: HSCT: Recommended daily oral dosage of PREVYMIS in pediatric patients 6 months to less than 12 years of age or 12 years of age and older and weighing less than 30 kg

Body weight	Daily oral dose	Tablets	Oral pellets
30 kg and above	480 mg	One 480 mg tablet or Two 240 mg tablets	Four 120 mg packets of oral pellets
15 kg to less than 30 kg	240 mg	One 240 mg tablet	Two 120 mg packets of oral pellets
7.5 kg to less than 15 kg	120 mg	Not recommended	One 120 mg packet of oral pellets
6 kg to less than 7.5 kg	80 mg	Not recommended	Four 20 mg packets of oral pellets

Instructions for Use should be followed for preparation and administration of PREVYMIS oral pellets.

Table 2: HSCT: Recommended daily IV dosage of PREVYMIS in pediatric patients 6 months to less than 12 years of age or 12 years of age and older and weighing less than 30 kg

Refer to **Prescribing Information** for IV preparation and administration dosing instructions.

Body weight	Daily IV dose
30 kg and above	480 mg
15 kg to less than 30 kg	120 mg
7.5 kg to less than 15 kg	60 mg
6 kg to less than 7.5 kg	40 mg

Selected Safety Information

PREVYMIS is contraindicated in patients receiving pimozide or ergot alkaloids.

- Increased pimozide concentrations may lead to QT prolongation and torsades de pointes.
- Increased ergot alkaloids concentrations may lead to ergotism.

PREVYMIS is contraindicated with pitavastatin and simvastatin when co-administered with cyclosporine. Significantly increased pitavastatin or simvastatin concentrations may lead to myopathy or rhabdomyolysis.

Selected Safety Information continues on next page.

CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplant; IV, intravenous.

HSCT: Dosage adjustment when co-administered with cyclosporine for pediatric patients 6 months to less than 12 years of age or 12 years of age and older and weighing less than 30 kg

- If oral or IV PREVYMIS is co-administered with cyclosporine in pediatric HSCT recipients 6 months to less than 12 years of age, the dosage of PREVYMIS may require adjustment (see **Table 3**)
  - If cyclosporine is initiated after starting PREVYMIS, the next dose of PREVYMIS should be the daily oral or IV dose co-administered with cyclosporine (see **Table 3**)
  - If cyclosporine is discontinued after starting PREVYMIS, the next dose of PREVYMIS should be the daily oral or IV dose administered without cyclosporine (see **Table 1** or **Table 2**)
  - If cyclosporine dosing is interrupted due to high cyclosporine levels, no dose adjustment of PREVYMIS is needed

Selected Safety Information (*continued*)

The concomitant use of PREVYMIS and certain drugs may result in potentially significant drug interactions, some of which may lead to adverse reactions (PREVYMIS or concomitant drugs) or reduced therapeutic effect of PREVYMIS or the concomitant drug.

Intravenous formulation of PREVYMIS contains the excipient hydroxypropyl betadex. PREVYMIS injection should be used only in patients unable to take oral therapy and patients should be switched to oral PREVYMIS as soon as they are able to take oral medications. If possible, intravenous administration should not exceed 4 weeks.

In patients with renal impairment, accumulation of hydroxypropyl betadex may occur. In adult patients with CLcr less than 50 mL/min and in pediatric patients with a similar degree of renal impairment (based on age-appropriate assessment of renal function) receiving PREVYMIS injection, closely monitor serum creatinine levels.

Animal studies have shown the potential for hydroxypropyl betadex to cause ototoxicity. The active ingredient, letermovir, is not known to be associated with ototoxicity.

The rate of adverse events occurring in at least 10% of adult HSCT recipients treated with PREVYMIS and at a frequency at least 2% greater than placebo were nausea (27% vs 23%), diarrhea (26% vs 24%), vomiting (19% vs 14%), peripheral edema (14% vs 9%), cough (14% vs 10%), headache (14% vs 9%), fatigue (13% vs 11%), and abdominal pain (12% vs 9%).

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Table 3: HSCT: Recommended dosage of PREVYMIS when co-administered with cyclosporine in pediatric patients 6 months to less than 12 years of age or 12 years of age and older and weighing less than 30 kg

Body weight	Daily oral dose	Tablets	Oral pellets	Daily IV dose
30 kg and above	240 mg	One 240 mg tablet	Two 120 mg packets of oral pellets	240 mg
15 kg to less than 30 kg	120 mg	Not recommended	One 120 mg packet of oral pellets	120 mg
7.5 kg to less than 15 kg	60 mg	Not recommended	Three 20 mg packets of oral pellets	60 mg
6 kg to less than 7.5 kg	40 mg	Not recommended	Two 20 mg packets of oral pellets	40 mg

Following the completion of PREVYMIS prophylaxis, monitoring for CMV reactivation in HSCT recipients is recommended.

Instructions for Use should be followed for preparation and administration of PREVYMIS oral pellets.

Refer to **Prescribing Information** for IV preparation and administration dosing instructions.

Selected Safety Information (*continued*)

Hypersensitivity reaction, with associated moderate dyspnea, occurred in one adult HSCT recipient following the first infusion of IV PREVYMIS after switching from oral PREVYMIS, leading to treatment discontinuation.

The most common adverse event occurring in at least 10% of adult kidney transplant recipients treated with PREVYMIS and at a frequency greater than valganciclovir was diarrhea (32% vs 29%).

Selected Safety Information continues on next page.

HSCT, hematopoietic stem cell transplant; IV, intravenous.

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Oral pellets 20 mg, 120 mg per packet

Preparation and administration of oral pellets

PREVYMIS oral pellets can be administered:

- Orally after mixing with soft food or
- Via NG tube or G tube.

Preparation and administration mixed with soft food

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

- Do not crush or chew PREVYMIS oral pellets
- Mix PREVYMIS oral pellets with 1 to 3 teaspoons of soft food (such as applesauce, yogurt, or pudding) that is at or below room temperature. Do not use hot food
- Administer entire mixture within 10 minutes of mixing PREVYMIS oral pellets with the soft food

Preparation and administration via NG tube or G tube

See **Instructions for Use**, **Table 4,** and **Table 5** for details on the preparation and administration of PREVYMIS oral pellets via NG tube or G tube.

1. Pour PREVYMIS oral pellets into a medicine cup containing room temperature water (see Initial volume in **Table 4** and **Table 5**).
   Do not mix PREVYMIS oral pellets with hot or cold (refrigerated) water.
2. Wait 10 minutes. Do not shake or swirl the medicine cup. PREVYMIS oral pellets will not dissolve but will become loose or broken up. The entire mixture should be administered (see steps 3 and 4) within 2 hours.
3. Stir the mixture with the syringe and administer entire mixture right away using the syringe and NG tube or G tube.
4. Add room temperature water (see Rinse volume in **Table 4** and **Table 5**) to the medicine cup for rinsing, stir with a syringe and administer the entire rinse mixture using the syringe and NG tube or G tube.
5. Flush the NG tube or G tube with the volume of water recommended by the NG or G tube manufacturer.

Selected Safety Information (*continued*)

The safety profile of PREVYMIS in pediatric subjects was consistent with the safety profile observed in clinical trials of PREVYMIS in adults.

If PREVYMIS is co-administered with cyclosporine, the dosage of PREVYMIS should be decreased to 240 mg once daily.

If PREVYMIS is co-administered with cyclosporine in pediatric patients less than 12 years of age, dose adjustment may be required.

Table 4: Recommendations for administration of PREVYMIS oral pellets via NG tube.

Dosage	NG tube[a]	Syringe type[b]	Mixing container	Initial volume (mL)	Rinse volume (mL)
120 mg to 480 mg	Any ≥8 Fr NG tube	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

Table 5: Recommendations for administration of PREVYMIS oral pellets via G tube.

Dosage	G tube[a]	Syringe type[b]	Mixing container	Initial volume (mL)	Rinse volume (mL)
120 mg to 480 mg	Any G tube	Appropriately sized ENFit or catheter-tipped syringe	Medicine cup	15	15
40 mg to 80 mg	Any 12 Fr G tube			3	2

[a]Fr = French; PUR = polyurethane.
[b]With ENFit syringe, a medicine straw (large bore) is needed to aid withdrawal of the mixture from the medicine cup.

Selected Safety Information (*continued*)

Co-administration of PREVYMIS may alter the plasma concentrations of other drugs and other drugs may alter the plasma concentrations of PREVYMIS. Consult the full Prescribing Information prior to and during treatment for potential drug interactions.

Closely monitor serum creatinine levels in patients with CLcr less than 50 mL/min using PREVYMIS injection.

Selected Safety Information continues on back cover.

G, gastric; NG, nasogastric.

Prescribing Information | Patient Information | Instructions for Use

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PREVYMIS is not recommended for patients with severe (Child-Pugh Class C) hepatic impairment.

The safety and effectiveness of PREVYMIS have not been established for:

- HSCT recipients less than 6 months of age or weighing less than 6 kg, or
- Kidney transplant recipients less than 12 years of age or weighing less than 40 kg.

For patients with creatinine clearance (CLcr) greater than 10 mL/min (by Cockcroft-Gault equation), no dosage adjustment of PREVYMIS is required based on renal impairment. The safety of PREVYMIS in patients with end-stage renal disease (CLcr less than 10 mL/min), including patients on dialysis, is unknown.

Before prescribing PREVYMIS® (letermovir), please read the accompanying Prescribing Information. The Patient Information and Instructions for Use also are available.

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