Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCINF038.1225	**ANTI-INFECTIVE AGENTS** **PREVYMIS®** (letermovir injectable)
Effective Date: 2/1/2026	**Review/Revised Date**: 02/18, 10/18, 10/19, 10/20, 07/21, 11/21, 11/22, 10/23, 12/23, 10/24, 11/25 (JEF)
Original Effective Date: 04/18	**P&T Committee Meeting Date**: 04/18, 12/18, 12/19, 12/20, 08/21, 12/21, 12/22, 10/23, 12/23, 12/24, 12/25
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For **initiation of therapy** (new start) to prevent cytomegalovirus (CMV) infection and disease, both of the following must be met:

1. One of the following:
    a. Patient is using for prophylaxis of cytomegalovirus (CMV) infection after allogeneic hematopoietic stem cell transplant (HSCT) and all of the following:
        i. Attestation patient (recipient of HSCT) is CMV seropositive (CMV R+) defined as detectable levels of CMV IgG antibody levels
        ii. Attestation that therapy will be started within 28 days post-transplantation
        iii. If requesting for prophylaxis beyond 100 days post-transplantation, documentation that the member is at high risk for late cytomegalovirus infection and disease must be provided (coverage for up to 200 days post transplantation will be allowed, see coverage duration)
    b. Patient is using for prophylaxis of CMV disease after kidney transplant and all of the following:

i. Patient (recipient of transplant) is at high risk, defined as CMV seropositive Donor in a Recipient that is CMV seronegative (CMV D+/R-)
ii. Attestation that therapy will be started within seven (7) days post-transplantation

2. Medical rationale provided for not using oral formulation (such as patient is unable to swallow)

For member **established on therapy** (within the previous year): Documentation of response to therapy and member is within 200 days post allogeneic or kidney transplant

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:
Age must be appropriate based on FDA-approved indication

PRESCRIBER RESTRICTIONS:
Must be prescribed by or in consultation with a hematologist, oncologist, or infectious disease specialist.

COVERAGE DURATION:
Authorization will be approved for up to 200 days post-transplant

---

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Letermovir works by inhibiting the production of proper unit length genomes and interfering with virion maturation. It inhibits the CMV DNA terminase complex (pUL51, pUL56, and pUL89), which is required for viral DNA processing and packaging.

FDA APPROVED INDICATIONS:

- 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)
- Prophylaxis of cytomegalovirus (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-])

POSITION STATEMENT:

Prophylaxis of CMV infection after allogeneic hematopoietic stem cell transplant

Current therapy for CMV in patients with allogeneic stem cell transplant is either prophylactic or preemptive. Prophylaxis involves administering medication to prevent infection for at-risk patients while preemptive therapy involves routine screening to detect early infection and administering medications early to avoid disease progression. The Center for Disease Control (CDC), Infectious Disease Society of America (IDSA), American Society for Transplantation and Cellular Therapy (ASTCT), and National Cancer Network (NCCN) all support the use of surveillance with pre-emptive therapy.

In allogeneic HCT recipients, NCCN recommends surveillance for at least three to six months after transplant in CMV IgG seropositive cases. For primary prophylaxis in seropositive patients, NCCN recommends considering therapy with letermovir. For preemption, NCCN recommends routine CMV surveillance with weekly monitoring by polymerase chain reaction (PCR). If CMV reactivation is detected, it is recommended to initiate therapy with oral valganciclovir or IV ganciclovir or IV foscarnet. Oral valganciclovir therapy is most commonly used, however some centers prefer ganciclovir. IV foscarnet and IV cidofovir may be used for cases of ganciclovir-resistant CMV or when ganciclovir is not tolerated (e.g., myelosuppression). NCCN notes that higher risk transplant subgroups may exist and require different management strategies.[8] The American Society for Transplantation and Cellular Therapy recommends that letermovir should be used as primary prophylaxis in CMV seropositive adults allogeneic HCT recipients. They also state that if letermovir prophylaxis cannot be used, CMV monitoring and PET is recommended over (val)ganciclovir or foscarnet as primary prophylaxis.[9] For CMV-seronegative HSCT recipients of seropositive donor cells (i.e., D-positive or R-negative), the Center for Disease Control (CDC) preferentially recommends for a preemptive approach against early CMV (i.e., <100 days after HSCT) over prophylaxis because of the low attack rate of active CMV infection if screened or filtered blood product support is used.[11] The American Society for Transplantation and Cellular Therapy do not limit use to CMV positive or CMV negative donors, but

state that all CMV D+/R- HCT recipients should be monitored due to the risk from transmission of CMV from donor to recipient via the stem cell product. They also state that the risk of CMV infection in CMV D-/R- HCT is relatively low.[9]

Risk factors for CMV infection and disease after HSCT include CMV seropositive recipient, acute-graft-versus host disease, requiring high dose of steroids, older age, T cell depletion, and certain donor sources such as haploidentical donor or cord blood transplant.[9]

Per package insert, letermovir may be continued through 100 days post-HSCT for CMV prophylaxis, and through 200 days in patients with increased risk of late CMV infection. Examples of risk factors for late CMV infection include 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.[1]

In a double-blind, phase three study (N=565), patients were randomized to receive either letermovir or placebo for 14 weeks for post-HSCT. Fewer patients in the letermovir group than in the placebo group had clinically significant CMV infection by week 24 after transplantation (122 of 325 patients [37.5%] vs. 103 of 170 [60.6%], P<0.001). Clinically significant CMV infection was defined as CMV disease or viremia leading to preemptive therapy. Amongst those who developed clinically significant CMV infection, most had CMV viremia rather than CMV disease. CMV viremia resulting in preemptive therapy occurred in 52 of 325 patients receiving letermovir (16.0%) and 68 of 170 patients receiving placebo (40.0%). CMV disease was roughly equivalent in both groups and occurred in 5 of 325 patients receiving letermovir (1.5 %) and 3 of 170 patients receiving placebo (1.8 %). All-cause mortality at week 24 was lower in the letermovir group compared to placebo (9.8% vs 15.9% respectively) but at 48 weeks after transplantation not significant (20.9% among letermovir recipients and 25.5% among placebo recipients [P=0.12]).

Prophylaxis of CMV infection after kidney transplant

The 2019 American Society of Transplantation guidelines for CMV in solid organ transplant recipients recommends valganciclovir, IV ganciclovir, and high dose valacyclovir for CMV prophylaxis in kidney transplant patients. Valganciclovir was noted to be the preferred agent due to improved bioavailability and lower pill burden. Use of acyclovir is not recommended for CMV prophylaxis. An extended duration of 200 days versus 100 days is recommended due to post prophylaxis delayed-onset CMV disease[10]. Letermovir may also be continued through 200 days post-kidney transplant for CMV prophylaxis.[1] At the time of publication, letermovir was not

approved for use in kidney transplant recipients but is mentioned as a possible future therapy.[10]

Risk factors for CMS disease after solid organ transplant include CMV-seronegative recipient who receives organ from a CMV-seropositive done (D+/R-), drug-induced immunosuppression, allograft rejection (especially when treated with lymphocyte depleting antibodies) and transplant type (highest risk with lung, small intestinal and vascularized composite allograft tissue).[10]

In a double-blind, phase three study (N=589), patients were randomized to receive either letermovir or valganciclovir for 28 weeks for post-kidney transplant. Letermovir group was noninferior to valganciclovir group for prevention of CMV disease through week 52 after transplant (30 of 289 patients [10.4%] vs. 35 of 297 [11.8%], 95% CI, −6.5% to 3.8%). CMV disease was confirmed by an independent masked adjudication committee, through post-transplant week 52 (prespecified noninferiority margin, 10%). Development of confirmed CMV occurred in 0 of 289 patients receiving letermovir (0.0%) and 5 of 297 patients receiving placebo (1.7%), [95% CI, −3.4% to 0.1%].

Dosing

- The recommended dose is 480 mg orally or intravenously once daily. Dosing should be adjusted when co-administered with cyclosporine. Letermovir injection should be used only in patients unable to take oral therapy and patients should be switched to oral letermovir as soon as they are able to take oral medications. Tablet and injection formulations may be used interchangeably, and no dose adjustment is necessary when switching formulations.
- For use after HSCT: Initiate letermovir 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, letermovir may be continued through Day 200 post-HSCT.
- For use after kidney transplant: Initiate letermovir between Day 0 and Day 7 post-transplant and continue through Day 200 post-transplant.

BILLING GUIDELINES AND CODING:

HCPCS	Coding Description	Brand Name
Medical Benefit		
J3490, C9399	Unclassified drugs or biologicals	Prevymis (Injectable)
ADMINISTRATION CODES◊		
96365	Ther/proph/diag iv inf init	

◊ Coding/Administration Notes:
• The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine

review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
• HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

REFERENCE/RESOURCES:

1. [Prevymis®] package insert. Whitehouse Station, NJ: Merck; January 2025.
2. [Prevymis®] In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically.
3. [Prevymis®] In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically.
4. Limaye AP, Budde K, Humar A, et al. Letermovir vs Valganciclovir for Prophylaxis of Cytomegalovirus in High-Risk Kidney Transplant Recipients: A Randomized Clinical Trial. JAMA. 2023;330(1):33-42.
5. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation. N Engl J Med. 2017 Dec 21;377(25):2433-2444.
6. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant. 2009 Oct;15(10):1143-238. doi: 10.1016/j.bbmt.2009.06.019. Erratum in: Biol Blood Marrow Transplant. 2010 Feb;16(2):294. Boeckh, Michael A [corrected to Boeckh, Michael J]. PMID: 19747629; PMCID: PMC3103296.
7. Boeckh M, Ljungman P. How we treat cytomegalovirus in hematopoietic cell transplant recipients. Blood. 2009 Jun 4;113(23):5711-9.
8. National Comprehensive Cancer Network® (NCCN), "Prevention and Treatment of Cancer-Related Infections," Version 3.2024.
9. Hakki M, Aitken SL, Danziger-Isakov L, et al. American Society for Transplantation and Cellular Therapy Series: #3—Prevention of Cytomegalovirus Infection and Disease After Hematopoietic Cell Transplantation. Transplantation and Cellular Therapy. 2021 Sept;27 (9):707-719.
10. Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients—Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019; 33:e13512. https://doi.org/10.1111/ctr.13512
11. Centers for Disease Control and Prevention; Infectious Diseases Society of America; American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Biol Blood Marrow Transplant. 2000;6(6a):7-83.