letermovir (Prevymis™)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO130

Description

Letermovir (Prevymis) is an orally administered antiviral agent that inhibits cytomegalovirus (CMV) deoxyribonucleic acid (DNA) terminase complex which helps prevent CMV infection in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT) and adult CMV-seronegative recipients of a kidney transplant from a seropositive donor [D+/R-].

Length of Authorization

- Initial: up to 200 days post-transplant
- Renewal: no renewal

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
letermovir (Prevymis)	240 mg tablet	Prophylaxis for CMV Infection Post-HSCT and Kidney Transplant	30 tablets/30 days
	480 mg tablet		

Initial Evaluation

I. **Letermovir (Prevymis)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist, hematologist, infectious disease, or transplant specialist; **AND**
   C. Member will be using letermovir (Prevymis) for the prevention of CMV infection or disease; **AND**
   D. Provider attestation that member is at high risk of CMV infection; **AND**
   E. The request is for letermovir (Prevymis 480 mg tablet); **OR**
      1. If the request is for letermovir (Prevymis) 240 mg, it will be used in combination with cyclosporine; **AND**
   F. A diagnosis of one of the following:
      1. **Allogeneic hematopoietic stem cell transplant (HSCT); AND**
         i. Member is cytomegalovirus (CMV)-seropositive HSCT recipient; **AND**
         ii. Documentation of transplant date has been recorded in chart notes; **AND**
         iii. Provider attestation that letermovir (Prevymis) will not be used past 100-days post-transplant; **OR**

a. If patient is at high-risk for late CMV infection, provider attests that letermovir (Prevymis) will not be used past 200-days post-transplant; **AND**
    i. Member has received, or will receive, letermovir (Prevymis) as primary prophylaxis during the first 100-days post-transplant; **OR**

2. **Kidney transplant; AND**
    i. Member is a CMV-seronegative kidney transplant recipient; **AND**
    ii. Kidney donor is CMV-seropositive; **AND**
    iii. Documentation of transplant date has been recorded in chart notes; **AND**
    iv. Provider attestation that letermovir (Prevymis) will be initiated between days 0 and 7 post-transplant; **AND**
    v. Provider attestation that letermovir (Prevymis) will not be used past 200 days post-transplant; **AND**
    vi. Member has an intolerance or contraindication to valganciclovir

II. Letermovir (Prevymis) is considered investigational when used for all other conditions, including but not limited to:
    A. Prevention of CMV infection or disease settings other than HSCT or kidney transplant
    B. Treatment for CMV infection or disease
    C. Prevention of CMV infection beyond 200 days post-transplant
    D. Pre-emptive therapy of CMV infection

Supporting Evidence

I. According to the prescribing information, letermovir (Prevymis) has only been FDA-approved in the setting of CMV prophylaxis in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT) and adult CMV-seronegative recipients of a kidney transplant from a CMV-seropositive donor [D+/R-]. Safety and efficacy in the pediatric population has not been established.

II. Considering the complexity of care for patients receiving HSCT or kidney transplant, the agent requested must be prescribed by, or in consultation with, an oncologist, hematologist, infectious disease, or transplant specialist.

III. The recommended dose of letermovir (Prevymis) according to the prescribing information is 480mg daily. If letermovir (Prevymis) is intended to be used in combination with cyclosporine as part of anti-rejection regimen, the dose of letermovir (Prevymis) should be reduced to 240mg

daily due to a drug-drug interaction that causes an increase in serum blood concentrations of both drugs.

IV. **Allogeneic hematopoietic stem cell transplant (HSCT)**

- The safety and efficacy of letermovir (Prevymis) was studied in a multicenter, double-blind, placebo-controlled, Phase 3 trial in adult CMV-seropositive recipients [R+] of those who have received an allogeneic hematopoietic stem cell transplant (HSCT). Of the 325 participants who received letermovir (Prevymis), 38% failed prophylaxis compared to 61% in the placebo arm [95% CI (32.5, 14.6)].
- A review by Chen et al. 2018 demonstrated that among the six antiviral therapies studied, ganciclovir and letermovir (Prevymis) were the most effective in reducing incidence of CMV reactivation when used as universal prophylaxis agents. Results further suggest that patients undergoing allogeneic HSCT would significantly benefit from universal prophylaxis with an agent that is tolerable after HSCT. The data suggest that although effective at reducing CMV reactivation and disease, ganciclovir use cannot be recommended as a universal prophylaxis agent because of an increased risk of myelosuppression and subsequent drug discontinuation. In contrast, the data suggests that letermovir (Prevymis) has an excellent safety profile with no myelosuppression, and its use should be considered for this indication in patients at risk. Letermovir (Prevymis) was associated with a decrease in CMV-related outcomes and all-cause mortality through 24 weeks after HSCT. Data around acyclovir found that although a delay in the onset of CMV reactivation was demonstrated, acyclovir showed nonsignificant efficacy in preventing CMV disease. Valacyclovir, which has a greater bioavailability than acyclovir was compared with acyclovir and found to be associated with a lower rate of viremia with similar rate of survival to acyclovir in CMV R+ or D+ allogeneic HCT recipients. High-dose acyclovir and valacyclovir are less myelosuppressive than ganciclovir and appear to have some efficacy for CMV prophylaxis, but these agents have inferior in vitro activity against CMV than ganciclovir. Though ganciclovir has promising efficacy, treatment is limited in this HSCT patient due to its increased risk of myelosuppression.
- Extended use of letermovir (Prevymis) post-HSCT up to 200 days was studied in a randomized, double-blind, placebo-controlled, phase 3 clinical trial of 218 patients who had been treated with 100-days of primary prophylaxis with letermovir (Prevymis). The primary efficacy endpoint of percentage of patients with clinically significant CMV infection from week 14 (~100 days) post-transplant through week 28 (~200 days) post-transplant was experienced in 2.8% of patients in the letermovir (Prevymis) group compared to 18.9% of patients in the placebo group (-16.1, 95% CI [-25.8 to -6.5]; p-value = 0.0005). Reported adverse events were in alignment with those reported in the pivotal clinical trials and no new safety concerns were observed.

- Patients enrolled in the extended use trial had high risk of CMV disease, and the prescribing information for letermovir (Prevymis) indicates that extended use up to 200 days post-transplant can be used in patients at risk for late CMV infection and disease. IDSA guidelines suggest that risk factors for late onset CMV disease include [D+/R-] serostatus, shorter courses of prophylaxis, higher levels of immunosuppression, and allograft rejection (i.e., graft versus host disease [GVHD]).

V. **Kidney Transplant**

- Letermovir (Prevymis) was evaluated in a randomized, active-controlled, double-masked, double-dummy, non-inferiority trial in 601 patients who were CMV-seronegative recipients of a kidney transplant from a CMV-seropositive donor [D+/R-]. Patients were randomized to receive letermovir (Prevymis) or valganciclovir (VGCV) for 28 weeks and were observed for 52 weeks. The primary efficacy outcome was incidence of CMV disease through week 52, which was exhibited in 10.4% of patients in the letermovir (Prevymis) group and 11.8% of patients in the VGCV group (stratum-adjusted difference, −1.4% [95% CI, −6.5% to 3.8%]). Notably, no patients in the letermovir (Prevymis) group developed CMV disease through week 28 compared to 5 patients (1.7%) in the VGCV group (stratum-adjusted difference, −1.7%[95%CI, −3.4%to0.1%]).
- The most commonly reported adverse events in the letermovir group were diarrhea (31.5%), tremor (18.2%), and urinary tract infection (14%), while the most common adverse event leading to discontinuation were neutropenia (1%) and leukopenia (1%). However, drug-related leukopenia and neutropenia occurred less often in the letermovir (Prevymis) group (11.3% and 2.7%, respectively) than in the VGCV group (37.0% and 16.5%, respectively). The safety profile of letermovir (Prevymis) appears to be favorable compared to VGCV.
- The Infectious Disease Society of America (IDSA) and Transplant Society guidelines on the management of CMV in solid organ transplant indicate that standard of care for CMV prevention in kidney transplant patients is extended use (200 days) of either ganciclovir (GCV) or VGCV. However, extended use of VGCV has been associated with higher rates of myelosuppression, manifesting primarily as leukopenia and neutropenia. Letermovir (Prevymis) may be considered appropriate in patients who are at a higher risk of myelosuppression given its favorable safety profile and observed lower risk of myelotoxicity.
- According to the prescribing information for letermovir (Prevymis), therapy should be initiated during the first week post-transplant and continued through day 200 post-transplant for all kidney transplant recipients.

Investigational or Not Medically Necessary Uses

I. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for the following indications below:
   A. Prevention of CMV infection or disease in all other settings EXCEPT HSCT or kidney transplant
   B. Treatment for CMV infection or disease
   C. Prevention of CMV infection beyond 200 days post-transplant
   D. Pre-emptive therapy of CMV infection

References

1. Prevymis [Prescribing Information]. Whitehouse Station, NJ: MERCK & CO, Inc. August 2023.
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4. Kotton CN, Kumar D, Caliendo AM, et al. The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation. Transplantation. 2018;102(6):900-931. doi:10.1097/TP.0000000000002191
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6. 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. doi:10.1001/jama.2023.9106

Policy Implementation/Update:

Action and Summary of Changes	Date
Added criteria for extended use post-HSCT and kidney transplant indications; Updated supporting evidence	09/2023
Removed requirement of valacyclovir or ganciclovir trial given reduced efficacy and/or safety in comparison to letermovir	10/2020
Policy created	11/2019