Letermovir (PREVYMIS): CMV Prophylaxis Post-Kidney Transplant
National Drug Monograph Addendum
June 2024

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL INFORMATION	**Description / MOA**	**Letermovir is an antiviral active against cytomegalovirus (CMV) which inhibits CMV DNA terminase complex. Not associated with cross-resistance to other anti-CMV agents. No activity against herpesviruses (HSV) or varicella zoster virus (VZV)**

	Indication Under Review[1]	• **Cytomegalovirus prophylaxis for High-Risk Kidney Transplant Recipients**
		• Approved in 2017 for prophylaxis after allogeneic hemopoietic stem-cell transplant (HSCT
		  ○ VANF committee voted in 2018 to keep nonformulary
		  ○ New data for HCST
		  ▪ extension to 200 days
		  ▪ real-world data

	Dosage Regimen	480 mg daily (PO or IV)
	Dosage Forms Under Review	Letermovir tablets and injection for intravenous use

	Summary of prior HSCT data	Phase 3, double-blind trial RCT (2:1) vs. placebo in high-risk allogeneic HSCT (n=570)
		• Recipient CMV + (R+) with undetectable CMV DNA
		• Excluded end-stage renal disease or severe hepatic insufficiency, drug interactions.
		• Primary endpoint: discontinuation of study drug for any reason
		  ○ Letermovir: 38%
		  ○ Placebo: 61%
		• Clinically significant CMV infection
		  ○ 18% vs. 41%
		• All-cause mortality lower at week 24, but not week 48
		• Safety: primarily gastro-intestinal

New Data Supporting LET in Hematopoietic Stem Cell Transplants

- LET was originally approved by the FDA in 2017 as CMV prophylaxis, based on results of 1 large phase 3 blinded trial versus placebo for 100 days.[2] In that study, 38% of LET and 61% of placebo patients failed prophylaxis through week 24, most notably due to development of clinically significant CMV infection or initiation of pre-emptive therapy for CMV.
- Since that time, additional efficacy data comes from study NCT03930615, which extended prophylaxis with LET from 100 days to 200 days.[3]
- A systematic review published in 2023 evaluated 30 studies of LET as primary CMV prophylaxis in HSCT patients.[4]
  - Included 29 observational studies + the Phase 3 trial above
  - Duration of prophylaxis ranged from 100 days to 1 year post-transplant
  - With regards to outcomes:
    - LET consistently reduced CMV infection (CMVi) and clinically significant CMVi (csCMVi)
    - Impact on CMV disease was seen in most studies that reported at 14 weeks
    - Impact on all-cause mortality was less consistent
- Theoretical risk that prolonged prophylaxis might delay CMV-specific cellular reconstitution, so optimal strategy (prophylaxis vs. pre-emptive therapy, and ultimate duration of prophylaxis) unclear.[5,6]

Table 1: Newer data for letermovir in HSCT

Study	Demographics	Efficacy results
Russo et al., 2024[3] Phase 3, DB, placebo-controlled RCT (2:1) **Inclusion:** adult D+/R- HSCT recipients who had received up to 100 days of LET prophylaxis and were high-risk for CMV based on donor properties, stem cell source, receipt of anti-thymocyte globulin or alemtuzumab or graft vs. host disease (GVHD) requiring ongoing corticosteroids **Exclusion:** severe hepatic disease, end-stage renal disease, treatment with other anti-CMV agents (in prior 7 days), history of CMV end-organ disease or on preemptive therapy for CMV prior to randomization **Treatments:** LET 480mg (IV or PO) daily or placebo for up to 100 additional days (dose decreased to 240mg if concomitant cyclosporine A) **Primary outcome**: Failure: Clinically significant CMV disease* from week 14 (100 days) to week 28 (200 days) **Secondary endpoints:** CMV disease through week 38, time to onset CMV disease, safety, resistance	Letermovir (n=144) Placebo (n=74) 64% LET / 58% placebo male 79% LET / 81% placebo white **Reason for HSCT (LET vs. placebo)**** • AML (42% vs. 41%) • ALL (16% vs. 12%) • MDS (12% vs. 8%) • Lymphoma (6% vs. 12%) • Myelofibrosis (6% vs. 7%) • Other (19% vs. 20%) **CMV + donor (60% vs. 76%)** **CMV + recipient (99% vs. 100%)** **Conditioning regimen** • Myeloablative (51% vs. 45%) • Reduced intensity (32% vs. 73%) **GVHD at study entry** • None (79% vs. 87%) • Acute (17% vs. 12%) **Use of immunosuppressants** • Tacrolimus (98% vs. 98%) • Mycophenolate (96% vs. 96%) • Steroids (95% vs. 93%) • Alemtuzumab (9% vs. 12%) • Anti-thymocyte glob (47% both) • Ex-vivo T cell depleted graft (10% both)	**Primary Outcome:** Failure week 14-28 LET 3% Placebo 19% Difference -16.1% (95% CI -26 to -7) **Clinically significant CMV disease** LET 1% Placebo 18% **Initiation of pre-emptive therapy** LET <1% Placebo 15% **CMV end-organ disease** LET < 1% vs. 3% **Secondary outcomes:** **Clinically sig. CMV disease week 14-28** LET 13% Placebo 19% **All-cause mortality week 14-28** LET 1% Placebo 1% **Resistance substitutions (RAS)** None with LET RAS (0/52) VGC 12% (8/66) *Post-hoc analysis impact LET on death at week 24 and week 48 suggested benefit of LET primarily in patients with cs-CMV infection[4]*
Liu et al.[6] Single-center, retrospective, cohort from patients receiving allogeneic-HSCT at Barnes-Jewish hospital 2016-2019. LET prophylaxis implemented in January 2018, including in some off-label populations. Primary endpoint was clinically-significant CMV infection (csCMVi) by day 180. Other endpoints: • csCMVi by days 100 and 365 • CMV disease • acute Graft vs. host disease (aGVHD) • overall survival and CMV-related mortality.	333 of 524 allo-HSCT patients had CMV D+ or R+ • 149 received LET 184 did not for median 90 days, **Demographics** (LET vs. no LET) CMV status D+/R+ (45% vs. 55%) D-/R+ (39% vs. 34%) D+/R- (21% vs. 18%) **First HSCT** (84% vs. 91%) • **90% in both groups had peripheral blood as source** **Conditioning regimen** • Myeloablative (52% vs. 59%) • Reduced intensity (34% vs 29%) **AML / MDS most common reasons for HSCT in both groups** **aGVHD prophylaxis** • Post-Tx cyclophos. (46% vs. 33%) • Tacrolimus/methotrex (49% vs. 60%) • Thymoglobulin (16% vs. 4%) **High-risk** (44% vs. 36%)	**Efficacy results: (LET vs. no LET)** **Primary endpoint: csCMVi by day 180** 20% vs. 39% (p<0.0001) Difference was also significant in D+/R+ cohort (p=0.002) **csCMVi by day 100** (8% vs. 35%) **csCMVi by day 365** (25% vs. 41%) Rapid rise in csCMVi after discontinuation of LET in both R+ groups **aGVHD:** No difference in incidence of grade 2-4 aGVHD **Overall mortality lower with LET in first 3 months** (10% vs. 20%) but similar at 12 months (48% vs. 49%), and 24 months (59% vs. 57%). On MV analysis, LET showed benefit on mortality day 0-99 but worsening day 180-364 after LET discontinued

**Clinically significant CMV disease = initiation of pre-emptive therapy or onset of CMV end-organ disease*

***AML = acute myeloid leukemia, ALL = acute lymphocytic leukemia, MDS = myelodysplastic syndrome*

Efficacy: CMV Prophylaxis in Kidney Transplantation

Letermovir vs Valganciclovir for Prophylaxis of Cytomegalovirus in High-Risk Kidney Transplant Recipients[7]

- Treatments: PO letermovir 480 mg daily (with acyclovir) or PO valganciclovir 900 mg daily up to 200 days post-transplant
    - **Primary Outcome:** CMV disease, through posttransplant week 52 (prespecified NI margin, 10%).
    - **Secondary Outcomes**
        - CMV disease through week 28
        - Time to onset of CMV disease through week 52

Table 2: Letermovir CMV Prophylaxis in Kidney-Transplant Patients

Study	Demographics	Efficacy results
Limaye et al., 2023[7] Phase 3, DB/active-controlled RCT **Inclusion:** adult D+/R- kidney transplant recipients **Exclusion:** severe hepatic disease, end-stage renal disease, prohibited medications, prior solid organ transplant, double kidney transplant, CMV disease within 6 months prior to randomization **Treatments:** LET 480mg daily (+ acyclovir) VGC 900mg daily Each up to 200 days **Primary outcome**: CMV disease through week 52 (NI margin 10%) **Secondary endpoints:** CMV disease through week 28, time to onset CMV disease, safety, resistance	Letermovir (n=289) Valganciclovir (n=297) 84% white race 72% male Donor type (LET vs. VGC) • Deceased (59% vs. 61%) • Living, unrelated (22% vs. 17%) • Living, related (19% vs. 21%) Use of lymphocyte-depleting induction • LET 46%, VGC 47% Use of immunosuppressants • Tacrolimus (98% vs. 98%) • Mycophenolate (96% vs. 96%) • Steroids (95% vs. 93%)	**Primary Outcome:** % of patients with CMV disease through week 52 LET 10.4% VGC 11.8% Difference -1.4% (95% CI -6.5 to 3.8) **CMV disease through week 28 (day 200)** LET 0% VGC 1.7% *3 patients with viremia on Rx* **Time to onset of CMV disease through week 52:** similar, beginning soon after drug discontinuation **Resistance substitutions (RAS)** None with LET RAS (0/52) VGC 12% (8/66)

Efficacy Summary of LET in SOT

- In a large blinded randomized controlled trial, LET was non-inferior to VGC as prophylaxis against CMV in high-risk kidney transplant recipients.[7]
    - Patients in both groups developed CMV disease soon after discontinuation of prophylaxis and the time course was similar between the groups.
    - No patients developed resistance-associated substitutions to LET vs. 12% of those receiving VGC
- In addition to the RCT, several observational cohorts describe use of LET for other indications in SOT patients, such as rescue therapy in patients not responding to therapy and prophylaxis in other organ transplants in patients with adverse events or nonresponse to VCG.[8,9]
    - A study from the University of Wisconsin allowed for conversion from VGC to LET if myelosuppression due to VGC occurred in high-risk abdominal transplants (most were kidney). Improved white blood cell count and decreased risk of GCSF use were noted. Only 3% needed mycophenolate reduction due to neutropenia vs. 12% in the period before LET use. None had CMV end organ disease.
    - Similar finding was noted in a cohort of lung transplant patients, where patients who were switched to LET due to intolerance were compared with a matched cohort of patients who received VCG for prophylaxis. In this study, CMV infection breakthrough, neutropenia and ability to restart or increase mycophenolate were all improved. An imbalance in 1 year all-cause mortality was documented (15% with LET vs. 4% with VGC but much of this was during the COVID-19 pandemic, which was the most common cause of death, and most LET patients were started just before or during the pandemic.

Safety of Letermovir

Allogeneic Stem Cell Transplant[1-6]

- In Phase 3 trial of allo-HSCT, GI adverse events most common. Vomiting (19% vs. 14%), edema (14% vs. 9%), cough (14% vs. 10%), cough (14% vs. 10%), headache (14% vs. 9%) and abdominal pain (12% vs. 9%) higher with LET than placebo.
    - Cardiac adverse events (LET vs. placebo) 13% vs. 6%, most commonly tachycardia
    - Atrial fibrillation 3% vs. 1%, most mild-moderate
    - Hematologic parameters were not different between LET and placebo (neutropenia, anemia or thrombocytopenia)
- Safety with extension to 200 days similar to the initial trial and led to discontinuation of study drug in 5% vs. 1%
    - Cardiac adverse events 4% in both groups

Kidney transplant study versus VGC[6]

- **Adverse events (AE) noted in 93% of both groups**
- **Drug-related AEs 20% with LET vs. 35% with VGC, difference -15% (95% CI -22 to -8)**
    - **Serious AEs (SAE) 1.4% with LET vs. 5% VGC, difference -3.7 (95% CI -7 to -1)**
- **Discontinuation due to adverse events in 4% of LET and 14% of VGC subjects, difference -9.4% (95% CI -14 to -2.4)**
- **Difference in adverse events driven largely by a significant decrease in leukopenia (11% vs. 33%) and neutropenia (3% vs. 17%), including a lower incidence of grade 3 or 4 decreases in neutrophils/leukocytes.**
- **Fatigue was reported in 6% with LET and 11% with VGC.**
- Other adverse events were not significantly different, including GI adverse events, or edema.
- Real world cohorts of patients receiving LET as CMV prophylaxis in solid-organ transplant program, often were a change due to adverse events of VGC and noted improvement or resolution of cytopenias and reduction in need for modification of immunosuppression. Even in studies without a control arm, discontinuation due to adverse events to LET was low.

Antiviral resistance

- In a Phase 2b, dose-ranging study, 12 subjects who experienced prophylaxis failure had isolates analyzed and 1 of 12 had a resistance-associated substitution (RAS) that confers reduction in susceptibility to LET.
- In initial trial in HSCT, 1 patient had breakthrough CMV viremia and had an RAS that confers resistance to LET[2] Data from 50
- In the phase 3 study extending duration from 100 to 200 days of LET, no LET RAS were identified in 32 samples from patients with prophylaxis failure (from both groups).
- In the final Phase 3 trial in kidney-transplant recipients, no known RAS were identified from sequence analysis of 52 LET treated subjects who experienced CMV disease or discontinued early with CMV viremia (versus 12% of subjects in the VGC group). Novel substitutions were noted at resistance associated positions at low frequencies, but the significance of those is unknown.
- Real world cohorts of LET CMV prophylaxis for HSCT

Table 3: Alternatives to LET

Agent	Formulary Status	Advantages	Disadvantages
Letermovir	NF TBD	Can be used as prophylaxis in HSCT vs. pre-emptive therapy, especially in very high-risk patients Available IV and PO Non-inferior to VGC for prevention of CMV in kidney transplant recipients, but with lower hematologic adverse events, and discontinuation No cross-resistance with other anti-CMV preventative drugs	Many significant drug-drug interactions Not active against other herpes viruses, so additional prophylaxis for HSV/VZV necessary. Currently not indicated for treatment of CMV disease May have low barrier to resistance Intravenous formulation has hydroxypropyl betadex ingredient – recommend changing to oral as soon as possible Limited safety database for uncommon adverse events
Ganciclovir	F	Can be used in patients with a non-functional GI tract Minimal drug-drug interactions Long history of use for prevention and treatment of CMV in variety of populations Activity against other common herpesviruses	Only available for IV administration, and has Significant myelosuppression which can preclude use or result in need for more toxic medications Requires dose adjustment in renal impairment Resistance increasingly common Cannot usually be used as prophylaxis in HSCT due to predictable cytopenia, especially neutropenia
Valganciclovir	F	Long history of use for prevention and treatment of CMV in variety of populations, including CMV prophylaxis in high-risk solid organ transplant patients Minimal drug-drug interactions Predictable absorption for oral administration Activity against other common herpesviruses Available as a low-cost generic preparation	High pill burden Significant myelosuppression which can preclude use or result in need for more toxic medications Requires dose adjustment in renal impairment Cannot usually be used as prophylaxis in HSCT due to predictable cytopenia, especially neutropenia

Place in Therapy

- Letermovir is a well-tolerated antiviral active against CMV, which offers an option to use prophylaxis in very-high risk allo-HSCT patients. Many centers have used pre-emptive therapy as the primary strategy for CMV prevention, given myelotoxicity of valganciclovir and need to use that agent as treatment. Only a small percentage of HSCT patients would be at high enough risk to warrant prophylaxis but in those few patients, benefits of primary prophylaxis may outweigh risks and costs.
- Valganciclovir has been the mainstay of CMV prophylaxis in high-risk solid organ transplant recipients, either as prophylaxis or pre-emptive therapy. Many patients tolerate this medication well, and given the long history of use, well-documented safety record, lack of significant drug-drug interactions, and low cost, it should remain the workhorse agent for this indication. A significant portion of patients, however, will have cytopenias that develop on VGC or CMV resistant to VGC and letermovir offers an opportunity to continue prophylaxis in high-risk patients, to minimize the adverse events of valganciclovir.

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