Criteria for Formulary Consideration of letermovir

Efficacy
Letermovir is approved by the Food and Drug Administration (FDA) for cytomegalovirus (CMV) disease prophylaxis in CMV-seropositive recipients (R+) of an allogeneic hematopoietic stem cell transplant (HSCT). The pivotal trial that led to its approval was a phase 3, parallel, multicenter, randomized, double-blind, placebo-controlled trial that assessed the proportion of patients, among patients without detectable CMV DNA at randomization, who had clinically significant CMV infection through week 24 post transplantation. Of the 495 patients with undetectable CMV DNA at randomization, there were less patients in the letermovir group versus placebo who 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). Based on this pivotal trial, letermovir prophylaxis demonstrated a significantly lower risk of clinically significant CMV infection compared to placebo in patients undergoing allogeneic HSCT. Additionally, no other regimen is FDA approved for the prophylaxis of CMV infection in HSCT recipients.

Safety
Warnings and precautions include but are not limited to: nausea, diarrhea, vomiting, peripheral edema, cough, headache, fatigue, and abdominal pain.

Of the 373 patients who received letermovir in the phase 3 trial, 97.9% experienced an adverse event. The most common adverse reactions associated with letermovir were nausea (26.5%), diarrhea (26%), rash (20.4%), abdominal pain (11.8%), decreased appetite (10.2%), acute kidney injury (9.7%), hypertension (8.3%), and constipation (7.2%). Additionally, letermovir is a moderate CYP3A inhibitor, CYP2C8 inhibitor, CYP2C9/19 inducer, and a substrate and inhibitor of OATP1B1/3 transporters; thus, it has many clinically significant drug interactions and contraindications.

Potential look-a-like medications: Prevnar, Prevpac

Uniqueness
Letermovir is a first-in-class antiviral agent that inhibits CMV replication by targeting the CMV DNA terminase complex (pUL51, pUL56, pUL89). Both the intravenous (IV) and oral (PO) dosage forms are indicated for the prophylaxis of CMV infection and disease in adult patients who are CMV-seropositive recipients of an allogeneic HSCT.

Cost

Medication Strength/Form	AWP	Inpatient cost per unit	Outpatient cost per unit
Letermovir 20 mg/mL SDPF (24 mL)	$15.62/mL	$217.84	$312.48
Letermovir 20 mg/mL SDPF (12 mL)	$31.25/mL	$217.86	$312.48
Letermovir 480 mg TABS (28 tablets)	$270.88/tablet	$225.73	$156.32
Letermovir 480 mg TABS (14 tablets)		$225.73	$156.32
Letermovir 240 mg TABS (28 tablets)	$270.88/tablet	$225.73	$156.69
Letermovir 240 mg TABS (14 tablets)		$225.73	$156.69

For a one-day supply of intravenous therapy most patients will require a dose that uses 1 vial of the 24 mL vials. The cost per day of intravenous therapy is $217.84 inpatient and $312.48 outpatient.

For a one-day supply of oral therapy most patients will require a dose that uses one 480 mg tablet. The cost per day of oral therapy is $225.73 inpatient and $156.32 outpatient.

Recommendations
Add to formulary with restrictions for use: No ID consult required for primary prophylaxis use in high-risk allo-HSCT. ID consult required for other indications (e.g., secondary prophylaxis, treatment, use in SOT).

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Introduction[1-8]

Letermovir is approved by the Food and Drug Administration (FDA) for cytomegalovirus (CMV) disease prophylaxis in CMV-seropositive recipients (R+) of an allogeneic hematopoietic stem cell transplant (HSCT). Letermovir was granted orphan drug status and approved by the FDA by priority review on November 8, 2017 based on the results of a pivotal phase 3 trial. It is also being studied for use as CMV prophylaxis in kidney transplant recipients; as a condition of approval, Merck is obligated to provide final results of a phase 3 study comparing letermovir with valganciclovir in adult kidney transplant recipients by June 2023. Emergency use has been described in the treatment of multidrug-resistant CMV in a lung transplant recipient.

No other regimen is FDA approved for the prophylaxis of CMV infection in HSCT transplant recipients. Historically, CMV disease in HSCT recipients was treated with ganciclovir; foscarnet is an alternative when cytopenias are present. Intravenous (IV) immunoglobulin is added in CMV pneumonia. The 2021 National Comprehensive Cancer Network (NCCN) guidelines for Prevention and Treatment of Cancer-Related Infections recommends active surveillance for at least 1 to 6 months post allogenic HSCT transplant in CMV IgG seropositive patients. NCCN also recommends considering letermovir with acyclovir in high-risk patients as primary prophylaxis for CMV seropositive allogenic HSCT recipients through day 100 post HSCT with continued CMV surveillance. The 2021 American Society of Transplantation and Cellular Therapy, in conjunction with the Transplant Infectious Disease Special Interest Group, recommend letermovir prophylaxis for adult CMV seropositive allogeneic HSCT recipients, to begin no later than 28 days after HSCT and continuing through day 100 post-transplant. Universal prophylaxis has not been widely used due to myelosuppression risk associated with anti-CMV antiviral agents, although guidelines advise use of prophylaxis in high-risk patients after engraftment.

Pharmacokinetics[1,8-11]

The oral bioavailability of letermovir was 94% when administered to healthy subjects without cyclosporine, 35% when administered to HSCT recipients without cyclosporine, and 85% when administered to HSCT recipients with cyclosporine. The median time to peak concentration is 45 minutes to 2.25 hours. Steady-state concentrations are reached within 9 to 10 days. Administration with food does not have a clinically meaningful effect on overall letermovir exposures but results in a slight increase in the peak letermovir concentration. Administration with cyclosporine resulted in increases in letermovir peak concentrations and total exposure, and a decrease in letermovir half-life.

Letermovir is 97% present as unchanged drug in the plasma. It is extensively plasma protein bound (99%). No major metabolites were detected in the plasma; UBT1A1/1A3 represents a minor metabolic pathway. The mean terminal half-life is 12 hours, although a terminal half-life of 16 and 28 hours was reported in healthy women administered single and multiple doses, respectively, of the IV formulation. The primary route of elimination is hepatic uptake (organic anion-transporting polypeptide 1B1/3 [OATP1B1/3]). The majority of the dose is excreted in the feces (93%, 70% unchanged), with a small fraction excreted in the urine (less than 2%).

Pharmacodynamics[1,8-11]

Letermovir area under the curve (AUC) was approximately 1.6 and 3.8-fold higher in subjects with moderate and severe hepatic impairment, respectively, compared to healthy subjects. Letermovir AUC was approximately 1.9 and 1.4-fold higher in subjects with moderate and severe renal impairment, respectively.

Age (18 to 78 years), gender, race (white vs nonwhite), and body weight (up to 100 kg) did not have a significant effect on letermovir pharmacokinetics.

Pharmacology[1,2,13-18]

Letermovir, a CMV antiviral, is an inhibitor of the CMV DNA terminase complex (pUL51, pUL56, and pUL89), which is required for viral, DNA processing and packaging. Letermovir affects the production of proper unit length genomes and interferes with virion maturation. No antagonism of effect, or synergy, was seen when letermovir was combined with other CMV DNA polymerase inhibitors (cidofovir, foscarnet, or ganciclovir). Cross-resistance with antiviral drugs with other mechanisms of action is unlikely. Letermovir is fully active against viral populations with substitutions conferring resistance to other CMV antivirals, including ganciclovir. Letermovir is highly selective for CMV, exerting no activity against other viruses (e.g. human adenovirus type 2, hepatitis B virus, HIV type 1, human influenza A virus [subtype H1N1, strain A/WSN/33], hepatitis C). No in vitro antagonism or synergy was observed when letermovir was combined with antivirals active against HIV.

CMV mutants with reduced susceptibility to letermovir have been isolated in cell culture, with the resistance mutations mapped to UL56. Resistance-associated mutations occur between amino acid positions pUL56 231 and 369. As a condition of approval, the FDA is requiring additional phenotype analysis of letermovir against human CMV mutants carrying select

pUL56 and pUL89 substitutions. In vitro studies have demonstrated emergency of UL89 mutations under letermovir exposure. An augmented resistance effect has also been observed with a UL51 mutation.

FDA Approved Indications[1]
Letermovir is approved by the FDA for cytomegalovirus (CMV) disease prophylaxis in CMV-seropositive recipients (R+) of an allogeneic hematopoietic stem cell transplant (HSCT).
Date of FDA approval: 11/08/2017

Clinical Trials[19,20]
Drug: Letermovir vs Placebo
Reference: Marty FM, et al, 2017 (P001 study)
Study Design: Phase 3, randomized, double-blind, placebo-controlled, multicenter study
Study Funding: Merck
Patients: 565 adult CMV-seropositive recipients of allogeneic HSCT; 70 had CMV viremia prior to study drug administration and were excluded from the efficacy analyses. The efficacy population included 325 subjects treated with letermovir and 170 subjects who received placebo. Engraftment had occurred in 36.5% of subjects at randomization. Median age was 53 years in the letermovir group and 54 years in the placebo group (range, 18 to 78 years); 56.6% and 60.4%, respectively, were male; 80.7% and 84.4% were white, and 10.7% and 9.4% were Asian. Risk for CMV disease was high in 32.4% and 28.1% of letermovir- and placebo-treated patients, respectively, and low in 67.6% and 71.9%. The most common primary reasons for transplant were acute myeloid leukemia (38.1% and 37.5%), myelodysplastic syndrome (16.9% and 11.5%), and non-Hodgkin lymphoma (12.6% and 14.6%). Myeloablative therapy was received by about 50% of subjects in each group; in addition, about 52% in each group were receiving cyclosporine and 42% tacrolimus. Exclusion criteria included receipt of antiviral agents with anti-CMV activity. All patients continued herpes virus prophylaxis with acyclovir, valacyclovir, or famciclovir according to local practice.
Intervention: Subjects were randomized (2:1) to receive letermovir 480 mg once daily orally or IV (or 240 mg when coadministered with cyclosporine) or placebo orally or IV, with randomization stratified by study site and risk level for CMV at the time of study entry. Letermovir or placebo was initiated any time from day 0 to day 28 posttransplant (median, day 9) and continued through week 14 posttransplant. At least one IV dose was received by 99 subjects treated with letermovir and by 48 treated with placebo; IV doses were administered at the discretion of the investigator for subjects unable to take oral therapy.
Results:
Primary End Point(s):

- Incidence of clinically significant CMV infection through week 24 posttransplant (prophylaxis failure) was 37.5% (122 of 325 subjects) with letermovir and 60.6% (103 of 170 subjects) with placebo (CMV risk stratum adjusted difference, −23.5%; 95% confidence interval [CI], −32.5% to −14.6%; *P*<0.001). This prevention of clinically significant CMV infection in the letermovir group was consistent between subjects at high and low risk for CMV disease. Patients who discontinued the study or had missing end point data at week 24 were considered to have prophylaxis failure; the proportion of patients discontinuing therapy or with missing data were similar in the 2 treatment groups. CMV disease occurred in 1.5% in the letermovir group and 1.8% in the placebo group.

Secondary End Point(s):

- Clinically significant CMV infection through week 14 occurred in 19.1% in the letermovir group and 50% in the placebo group (CMV risk stratum adjusted difference, −31.3%; 95% CI, −39.9% to −22.6%; *P*<0.001).
- Time to clinically significant CMV infection in the primary end point population was prolonged in the letermovir group compared with the placebo group (*P*<0.001).

Other End Point(s):

- All-cause mortality at week 24 after transplantation was 10.2% in the letermovir group and 15.9% in the placebo group (*P*=0.03).
- All-cause mortality at week 48 after transplantation was 20.9% in the letermovir group and 25.5% in the placebo group (*P*=0.12).
- Engraftment rates and time to engraftment did not differ between treatment groups.
- Graft-versus-host disease frequency and intensity did not differ between treatment groups.
- Rates of other infections did not differ between treatment groups.

Comments: The study was conducted at 67 centers in 20 countries. An earlier phase 2 study (N=131) demonstrated a reduced incidence of CMV infection in allogeneic HSCT recipients treated for 12 weeks after engraftment with letermovir 240 mg once daily compared with placebo. Lower doses were reported to be suboptimal, allowing emergence of resistance mutations and viral breakthrough. The P001 study demonstrated a reduction in incidence of CMV viremia requiring preemptive treatment in patients treated with letermovir; long-term improvements in outcomes were not demonstrated and would require study in a larger population and for a longer duration of follow-up. Merck has committed to conducting a randomized, double-blind, placebo-controlled trial in CMV-seropositive recipients of allogeneic HSCT to evaluate the occurrence of late clinically significant CMV infection when prophylaxis is extended from 100 to 200 days.

A post-hoc analysis of this trial's data related to all-cause mortality was completed and published by Ljungman et al 2019. The two tables below show the all-cause mortality analysis comparing letermovir (LTV) to placebo. An analysis was also completed on those that did and did not develop csCMV infection in both the placebo and LTV arms. The hazard ratio for mortality was statistically significant in the placebo group compared to a non-statistically significant hazard ratio in the LTV group.

All-cause mortality	LTV	Placebo	P value
Week 24	12.1% 95% CI (8.6-15.7)	17.2% 95% CI (11.5-22.9)	0.04
Week 48	23.8% 95% CI (19.1-28.5)	27.6% 95% CI (20.8-34.4)	0.21

All-cause mortality	Hazard Ratio
Week 24: Adjustments for age, baseline risk, acute GVHD grades II-IV	0.58 95% CI (0.35-0.98), P=0.04
Week 48: Adjustments for age, baseline risk, acute GVHD grades II-IV	0.74 95% CI (0.49-1.11) P=0.14

Limitations: Size and duration of the study were inadequate to determine long-term benefits. Results from the longer duration study may not be available until 2023.

Off-Label[3,21]

One additional clinical trial addresses off-label CMV pre-emptive therapy in kidney or kidney-pancreas transplant recipients with letermovir versus standard of care. This phase 2 randomized, controlled, multicenter, open-label study was conducted to assess and determine the efficacy of letermovir defined as a decline in CMV DNA versus baseline within a 14-day treatment period. Patients were randomized to receive letermovir 40 mg PO twice daily, letermovir 80 mg PO daily, or local standard of care with valganciclovir (variable dosage regimens) for 14 days of therapy. Of the 27 patients included, 25 patients completed all 14 days of therapy with 2 patients discontinuing based on investigator decision. There were no reported cases of CMV disease, and all treatment groups experienced a statistically significant decrease from baseline CMV DNA viral load by day 15 (40 mg BID, P – 0.031; 80 mg QD, P = 0.018; standard of care, P = 0.001). There was no statistically significant difference between groups; however, the standard of care group saw a decline in CMV DNA viral load by day 4 whereas a similar decline was not seen until day 11 to 15 in the letermovir groups. By day 14, viral clearance was achieved in 50% of the patients in both the letermovir 40 mg PO twice daily group and letermovir 80 mg PO daily group, while only 28.6% of patients in the standard of care group achieved viral clearance. Letermovir was well tolerated, but it's relevant to note a lower dose of letermovir was used based on pharmacokinetic and pharmacodynamic data available at the time.

Clinical trials reviewing letermovir's use in solid organ transplant, including heart, kidney, and lung, are currently underway. In addition, letermovir's use in pediatric patients who undergo allogeneic HSCT and its potential use for treatment of resistant or refractory CMV infection are also being reviewed.

Warnings, Precautions, and Adverse Effects[1,19]

CONTRAINDICATIONS:

Letermovir is contraindicated in patients receiving pimozide or ergot alkaloids. Letermovir inhibits cytochrome P450 (CYP-450) 3A4. Coadministration with pimozide may result in increased pimozide concentrations, which may lead to QT prolongation and torsades de pointes. Coadministration with ergot alkaloids may result in increased concentrations of the ergot alkaloids (ergotamine and dihydroergotamine), which may lead to ergotism.

Letermovir is also contraindicated with pitavastatin and simvastatin when coadminsitered with cyclosporine. The combination of letermovir and cyclosporine may result in increased pitavastatin and simvastatin concentrations, which may lead to myopathy or rhabdomyolysis.

A potential contraindication is hypersensitivity to letermovir or any of its inactive ingredients (tablets contain colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and povidone 25; film coating contains hypromellose 2910, iron oxide red [only for 480 mg tablets], iron oxide yellow, lactose monohydrate, titanium dioxide, and triacetin, with Carnauba wax added as a polishing agent; injection contains hydroxypropyl betadex, sodium chloride, sodium hydroxide, and water for injection).

WARNINGS AND PRECAUTIONS:

Adverse reaction risk may be increased or therapeutic effect reduced as a result of drug interactions with letermovir.

In patients with creatinine clearance (CrCl) less than 50 mL/min, accumulation of the letermovir IV vehicle hydroxypropyl betadex can occur. Serum creatinine levels should be monitored closely.

No dosage adjustment is necessary in patients with CrCl greater than 10 mL/min; safety has not been evaluated in patients with end-stage renal disease, including those on dialysis.

No dosage adjustment is necessary in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. Use is not recommended in patients with severe (Child-Pugh class C) hepatic impairment.

There are no data regarding the effects of letermovir on human fertility; however, decreased fertility due to testicular toxicity was observed in male rats.

There are no adequate and well-controlled studies of letermovir in pregnant women. In animal reproductive studies, fetal malformations were observed at letermovir exposures 2 to 11 times higher than exposures associated with the recommended human dose.

Caution should be used when administering letermovir to a breastfeeding woman. No studies have been conducted to assess the presence of letermovir in human milk or its effects on breastfeeding infants or milk production.

Safety and efficacy of letermovir have not been established in pediatric patients. The pivotal trial included 56 patients aged 65 years and older. The safety and efficacy in the geriatric population (15% of study population) was similar to the efficacy in younger patients.

ADVERSE REACTIONS:
The most common adverse events reported during letermovir therapy, and more frequently with letermovir than placebo, include nausea, diarrhea, vomiting, peripheral edema, cough, headache, fatigue, and abdominal pain. The frequencies of these adverse events are summarized in Table 1 and laboratory abnormalities in Table 2.

Table 1. Adverse Events With Letermovir (Incidence ≥ 10% and Frequency ≥ 2% Greater than Placebo) in HSCT Recipients

Adverse Reactions	**Letermovir (n=373)**	**Placebo (n=192)**
Nausea	27%	23%
Diarrhea	26%	24%
Vomiting	19%	14%
Peripheral edema	14%	9%
Cough	14%	10%
Headache	14%	9%
Fatigue	13%	11%
Abdominal Pain	12%	9%

Table 2. Laboratory Abnormalities in HSCT Recipients Receiving Letermovir

Laboratory Test	**Letermovir (n=373)**	**Placebo (n=192)**
Absolute neutrophil count		
< 500 cells/mcL	19%	19%
500 to < 750 cells/mcL	4%	7%
750 to < 1000 cells/mcL	8%	9%
Hemoglobin		
< 6.5 g/dL	2%	1%
6.5 to < 8 g/dL	14%	15%
8 to < 9.5 g/dL	41%	43%
Platelets		
< 25,000 cells/mcL	27%	21%
25,000 to < 50,000 cells/mcL	17%	18%
50,000 to < 100,000 cells/mcL	20%	30%
Serum creatinine		
> 2.5 mg/dL	2%	3%
> 1.5 to 2.5 mg/dL	17%	20%

Interactions[1]

Letermovir is a substrate of OATP1B1/3 transporters. Coadministration with drugs that inhibit OATP1B1/3 transporters may result in increases in letermovir plasma concentrations, and thus an increase in adverse events. In vitro studies also suggest letermovir is a substrate of CYP3A, CYP2D6, UGT1A1, UGT1A3, and the P-glycoprotein transporter. Changes in letermovir concentrations due to inhibition of P-glycoprotein or UGTs are not expected to be clinically relevant.

Letermovir is a moderate inhibitor of CYP3A and OATP1B1/3 transporters. Coadministration with drugs that are CYP3A substrates or substrates of OATP1B1/3 transporters may result in increases in plasma concentrations of the coadministered substrates, resulting in an increase in adverse events.

Letermovir is an inducer of CYP2C9 and CYP2C19 and may reduce plasma concentrations of substrates of those pathways. In vitro, letermovir is also an inducer of CYP2B6; however, the clinical relevance of this interaction is unknown.

Potentially clinically important drug interactions are summarized in Table 3. In clinical drug-drug interaction studies, no clinically relevant interactions were observed between letermovir and acyclovir, digoxin, mycophenolate mofetil, posaconazole, ethinyl estradiol, and levonorgestrel.

Table 3. Drug Interactions With Letermovir

Drug	Effect	Clinical Recommendations
Amiodarone	Increased amiodarone	Monitor amiodarone concentrations, and monitor for amiodarone adverse events.
Atorvastatin	Increased atorvastatin	Do not exceed an atorvastatin dose of 20 mg daily; monitor closely for myopathy and rhabdomyolysis. Avoid concurrent use with cyclosporine.
Cyclosporine	Increased cyclosporine Increased letermovir	Decrease letermovir dose to 240 mg once daily. Monitor cyclosporine concentrations during treatment and after letermovir discontinuation and adjust cyclosporine dose accordingly.
CYP3A substrates (e.g., alfentanil, fentanyl, midazolam, quinidine)	Increased CYP3A substrate	Refer to dosing recommendations for the CYP3A substrate administered with a moderate CYP3A inhibitor (or strong CYP3A inhibitor if coadministered with cyclosporine). The CYP3A substrates pimozide and ergot alkaloids are contraindicated.
Dihydroergotamine	Increased dihydroergotamine	Contraindicated.
Ergotamine	Increased ergotamine	Contraindicated.
Fluvastatin	Increased fluvastatin	Consider fluvastatin dose reduction; monitor closely for myopathy and rhabdomyolysis.
Glyburide	Increased glyburide	Monitor glucose concentrations.
Lovastatin	Increased lovastatin	Consider lovastatin dose reduction; monitor closely for myopathy and rhabdomyolysis. Not recommended with concurrent cyclosporine.
Omeprazole	Decreased omeprazole	Monitor clinical response and adjust dose if needed.
Pantoprazole	Decreased pantoprazole	Monitor clinical response and adjust dose if needed.
Phenytoin	Decreased phenytoin	Monitor phenytoin concentrations.
Pimozide	Increased pimozide	Contraindicated.
Pitavastatin	Increased pitavastatin	Not recommended; contraindicated with concurrent cyclosporine.
Pravastatin	Increased pravastatin	Consider pravastatin dose reduction; monitor closely for myopathy and rhabdomyolysis.
Repaglinide	Increased repaglinide	Monitor glucose concentrations; avoid coadministration with cyclosporine.
Rifampin	Decreased letermovir	Coadministration not recommended.
Rosiglitazone	Increased rosiglitazone	Monitor glucose concentrations.
Rosuvastatin	Increased rosuvastatin	Consider rosuvastatin dose reduction; monitor closely for myopathy and rhabdomyolysis.
Simvastatin	Increased simvastatin	Not recommended; contraindicated with concurrent cyclosporine.

Sirolimus	Increased sirolimus	Monitor sirolimus whole blood concentrations during treatment and after letermovir discontinuation, adjusting sirolimus dose accordingly. Consult sirolimus dosing recommendations if receiving concurrent letermovir, cyclosporine, and sirolimus.
Tacrolimus	Increased tacrolimus	Monitor tacrolimus whole blood concentrations during treatment and after letermovir discontinuation, adjusting tacrolimus dose accordingly.
Voriconazole	Decreased voriconazole	Closely monitor for reduced voriconazole effectiveness.
Warfarin	Decreased warfarin	Monitor international normalized ratio.

Dosage and Administration[1]
The recommended dosage of letermovir is 480 mg orally or IV once daily. Letermovir prophylaxis should be initiated between day 0 and day 28 post-transplantation (before or after engraftment) and continued through day 100 post-transplantation. Dosage adjustment is required when letermovir is coadministered with cyclosporine.

Letermovir tablets may be administered with or without food but must be swallowed whole. The injection should be administered by IV infusion via a peripheral catheter or central venous line at a constant rate over 1 hour; bolus administration is not recommended. The injection contains hydroxypropyl betadex, and therefore should only be used in patients unable to take oral therapy. Patients should be switched to oral letermovir as soon as they are able to take oral medications. The oral tablets and injection may be used interchangeably, with no dosage adjustment necessary when switching formulations.

When coadministered with cyclosporine, the letermovir dosage should be decreased to 240 mg once daily. 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 interrupted due to high cyclosporine levels, no dosage adjustment of letermovir is necessary.

Letermovir injection must be diluted prior to IV administration. The contents of 1 vial may be added to a 250 mL prefilled IV bag containing sodium chloride 0.9% injection or dextrose 5% injection; only these 2 injection solutions are known to be chemically and physically compatible with letermovir injection.

Letermovir solution must be administered using one of the following compatible IV bags and infusion set materials: polyvinyl chloride (PVC), ethylene vinyl acetate, and polyolefin (polypropylene and polyethylene) IV bags; PVC, polyethylene, polybutadiene, silicon rubber, styrene-butadiene copolymer, styrene-butadiene-styrene copolymer, or polystyrene infusion set materials; diethylhexyl phthalate, tris (2-ethylhexyl) trimellitate, and benzyl butyl phthalate plasticizers; and radiopaque polyurethane catheters. Letermovir injection is not recommended for use with polyurethane-containing IV administration set tubing. The prescribing information should be consulted for a list of compatible and incompatible drug products.

No letermovir dosage adjustment is necessary in patients with CrCl greater than 10 mL/min. There is insufficient data to guide dosing in patients with CrCl of 10 mL/min or less or in patients on dialysis. Patients with CrCl less than 50 mL/min treated with letermovir injection may experience accumulation of the hydroypropyl betadex vehicle; serum creatinine should be closely monitored in these patients.

No letermovir dosage adjustment is necessary in patients with mild or moderate hepatic impairment. Use is not recommended in patients with severe hepatic impairment.

Monitoring Parameters[1]
Monitoring for CMV reactivation is recommended following completion of letermovir prophylaxis; serum creatinine (especially in patients with CrCl less than 50 mL/min [due to potential accumulation of IV vehicle hydroxypropyl betadex]).

How Supplied/Cost[1,22]
Letermovir is available as a sterile, preservative-free solution for IV infusion and tablets for oral administration. The IV solution is available in 30 mL single-dose vials of letermovir 20 mg/mL. There are two vial sizes: 24 mL (480 mg) and 12 mL (240 mg) vials. Vials should be stored at a controlled room temperature, 20 to 25°C, and protected from light. The IV solution is diluted prior to administration by adding the contents of the vial into a 250 mL bag of either 0.9% sodium chloride injection of 5% dextrose injection. Mix contents gently and avoid shaking vials and diluted IV bags. Letermovir is not compatible with polyurethane-containing IV administration sets. The diluted solution can be stored at room temperature for up to 24 hours or refrigerated, 2 to 8°C, for up to 48 hours. This time should include the duration of the infusion, which is 1 hour.

The oral, film-coated tablets are available in unit-dose blister card packages containing either 14 or 28 tablets. Tablets should be stored at controlled room temperature, 20 to 25°C.

Table 4. Cost of Letermovir Per Unit

Medication Strength/Form	AWP	Inpatient cost per unit	Outpatient cost per unit
Letermovir 20 mg/mL SDPF (24 mL)	$15.62/mL	$217.84	$312.48
Letermovir 20 mg/mL SDPF (12 mL)	$31.25/mL	$217.86	$312.48
Letermovir 480 mg TABS (28 tablets)	$270.88/tablet	$225.73	$156.32
Letermovir 480 mg TABS (14 tablets)		$225.73	$156.32
Letermovir 240 mg TABS (28 tablets)	$270.88/tablet	$225.73	$156.69
Letermovir 240 mg TABS (14 tablets)		$225.73	$156.69

AWP = average wholesale price

For a 100 day supply of inpatient therapy, most patients will require a dose that uses 1 vial daily of the 24 mL vials ($217.84) for a total cost of $21,784.

For a 100 day supply of outpatient therapy, most patients will require a dose that uses 1 of the 480 mg tablets daily ($156.32) for a total cost of $15,632.

Utilization[23]

A medication use evaluation was completed on hospitalized patients who received letermovir at Nebraska Medicine between 1/1/2018 to 6/30/2021. The results are described below in Tables 5-8.

Table 5. Baseline characteristics of patients on letermovir

Characteristics	All patients (n=11)
Age, median, years (range)	61 (17-74)
Male, n (%)	8 (73%)
Weight, median, kg	75.8 (59-94)
Transplant group	
HSCT	8
SOT	3
CMV risk	
High[a]	11
Low[b]	0
Indication for letermovir	
Primary prophylaxis	1
Secondary prophylaxis	7
Treatment	3
CMV resistance testing, n (%)	6 (55%)
Time to start letermovir s/p transplant, median, days (range)	109 (0-547)
Duration on letermovir, median, days (range)[c]	11 (1-470)
Inpatient duration on letermovir, average, days (range)	7 (0-19)
Outpatient duration on letermovir, average, days (range)	45 (0-451)
Total courses of letermovir therapy, n	18
Total courses of inpatient letermovir therapy, n	12
Inpatient duration of courses of therapy, median, days (range)	6 (4-15)

HSCT = hematopoietic stem cell transplant, SOT = solid organ transplant

[a] high risk: CMV recipient positive, haploidentical, mismatch, ex vivo T-cell depleted graft, cord blood, graft versus host disease requiring 0.5 mg/kg steroids before day 28, antithymocyte globulin or alemtuzumab conditioning, repeat HSCT or donor lymphocyte infusion

[b] low risk: all other patients

[c] Duration calculated as total days on letermovir including inpatient and outpatient therapy

Table 6. Baseline characteristics of **HSCT** patients on letermovir

Characteristics	HSCT patients (n=8)
Age, median, years (range)	63 (42-74)
Male, n (%)	7 (88%)
Weight, median, kg	76 (59-94)
Cancer diagnosis	
AML	2
MDS	2
T-cell related leukemia	3
Myelofibrosis	1
HLA matching and donor type	
Matched unrelated	4
Matched related	3
Mismatched related	0
Mismatched unrelated	0
Haploidentical	1
Stem cell source	
Peripheral blood	8
Bone marrow	0
Cord blood	0
CMV status	
Donor + / Recipient +	2
Donor - / Recipient -	0

Donor + / Recipient -	0
Donor - / Recipient +	6

HSCT = hematopoietic stem cell transplant, AML = acute myeloid leukemia, MDS = myelodysplastic syndrome

Table 7. Baseline Characteristics of **SOT** patients on letermovir

SOT Characteristics	**SOT patients (n=3)**
Age, median, years (range)	44 (17-63)
Male, n (%)	1 (33%)
Weight, median, kg	76 (60-86)
SOT type	
Kidney	2
Multi-organ	1
CMV status	
Donor + / Recipient +	0
Donor - / Recipient -	0
Donor + / Recipient -	3
Donor - / Recipient +	0

SOT = solid organ transplant

Table 8. Clinical outcomes for Nebraska Medical Center patients on letermovir

Outcome	**All patients**
Breakthrough CMV infection on prophylaxis, n (%)[a]	3/8 (37.5%)
Resistant/refractory CMV treatment failure, n (%)[b]	2/3 (67%)

[a] Defined as CMV infection while patient is on appropriate prophylaxis (asymptomatic infection or CMV disease)
[b] Defined as inability to decrease CMV viral load and switch to different treatment agent

Table 9. Clinical outcomes for courses of therapy on letermovir based on transplant type

Outcome	**HSCT**	**SOT**	**Total courses of therapy**
Breakthrough CMV infections on prophylaxis, n (%)			
Prophylaxis	4/15 (26.7%)	^	15
Primary	1/2 (50%)	^	2
Secondary	3/13 (23.1%)	^	13
Resistant/refractory CMV treatment failure, n (%)	+	2/3 (67%)	3

HSCT = hematopoietic stem cell transplant, SOT = solid organ transplant
^ 0 patients who received a SOT were placed on letermovir for CMV prophylaxis (primary or secondary)
+ 0 patients who received a HSCT were placed on letermovir for resistant/refractory CMV treatment

As seen in Tables 5-9, of the 11 patients administered letermovir, 11 were classified as high risk for CMV. The indications for utilizing letermovir were, primary prophylaxis (n=1), secondary prophylaxis (n=7), and treatment (n=3). Of the 8 unique patients on letermovir, 3 (37.5%) experienced breakthrough CMV infection while on prophylaxis and of the 3 unique patients on letermovir for treatment, 2 (67%) experienced treatment failure. The 1 unique patient that was treated for resistant/refractory CMV with letermovir that did not experience treatment failure was on a regimen of letermovir 480 mg PO BID for 43 days. Of the 43 days of total therapy, 13 days were inpatient, and 30 days were outpatient treatment days. Of the 11 unique patients treated with letermovir, 5 patients each had 2 courses of therapy and 1 patient had 3 courses of therapy. Additionally, of the 18 courses of therapy, 10/18 (55.6%) of the courses of therapy were initiated inpatient. Finally, of the 18 courses of therapy, 9/18 (50%) of the patients continued therapy in the outpatient setting.

Pharmacoeconomic Analysis
Several pharmacoeconomic analyses have been conducted for primary prophylaxis. Many show that letermovir is cost-effective based on the thresholds set. It should be noted that the pharmacoeconomic analyses are largely based on the results of Marty et al, 2017 and have potential conflicts of interest (e.g., Merck funding/support). See appendix C.

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Appendix: Summary of Safety Issues and Implications for Pharmacy Operations

Characteristic	Summary
Medication Information	
Drug generic name (brand name)	Letermovir (Prevymis)
Drug manufacturer	Merck Sharp & Dohme Corp.
Schedule of medication	n/a
Route of administration	Oral, intravenous
Preparation (for pharmacy personnel)	The letermovir vial is diluted to a 250 mL pre-filled IV bag containing either 0.9% sodium chloride injection or 5% dextrose injection and mixed gently. Do not shake to mix the contents.
Is bedside dilution appropriate?	No ☒ Yes ☐
Stability	The diluted solution of letermovir can be stored for up to 24 hours at room temperature or up to 48 hours under refrigeration at 2 to 8°C. This time includes the duration of the infusion. The oral tablets should be stored at controlled room temperature at 20 to 25 °C in its original packaging.
Recommended storage conditions for medication, and how to manage excursions outside these conditions	See above
Does the manufacturer require patients to meet specific criteria for treatment with this medication? If so, where may healthcare providers find these criteria?	No
Operations Information	
Is filtration required during preparation or administration of the IV medication? *If **yes** for administration, ensure Willow adds filter information to admin instructions*	No ☒ Yes ☐ N/A ☐
Can medication doses be sent to patient care units via pneumatic tube system? See IC24. *If **no**, and not already addressed in IC24, add to policy IC24—contact Theresa Micheels.*	No ☒ Yes ☐ N/A ☐ Vials – no, do not shake Tablets – yes
Does the manufacturer have a restricted or special distribution program? If so, how may healthcare providers contact the program?	No ☒ Yes ☐
Safety/Policy Information	
Will this impact a dynamic alternative alert?	No ☒ Yes ☐ Letermovir is in the subclass: CMV antiviral agent – terminase complex inhibitors. Valganciclovir, foscarnet, cidofovir, and ganciclovir are in a different CMV antiviral agent subclass (nucleoside analog, inorganic pyrophosphate analog, nucleotide analog).
Is the medication (brand name, generic name, product packaging) similar to any other medications on the Institute for Safe Medication Practices (ISMP) Look-Alike-Sound-Alike (LASA)) list or confused names list? If not, is the medication expected to be added to the list? https://www.ismp.org/tools/tallmanletters.pdf http://www.ismp.org/Tools/confuseddrugnames.pdf	No ☒ Yes ☐ Potential look-a-like medications: Prevnar, Prevpac
Does the product package insert currently have any boxed warnings? For what?	No ☒ Yes ☐
Is this medication a hazardous agent? *If **yes**, Med Safety to update policy MM10 Attachment A*	No ☒ Yes ☐
Is this medication classified as chemotherapy per AHFS 10:00? *If **yes**, Drug Policy to update policy MM11 Attachment A*	No ☒ Yes ☐
Is the medication a vesicant or irritant? *If **yes**, ensure Willow flags as vesicant or irritant on MAR.*	No ☒ Yes ☐

Is this a high-alert medication that requires an indication? See MM02. *If **yes**, Med Safety to update policy MM02*	No ☒ Yes ☐ It is an antimicrobial agent which requires an indication for use.
Are there contraindications or significant warnings against medication use?	No ☐ Yes ☒ Concomitant use with the following drugs are contraindicated: • Ergot alkaloids • Pimozide • Pitavastatin plus cyclosporine • Simvastatin plus cyclosporine
Is special administration or monitoring recommended when starting therapy with this medication (e.g., Telemetry, BPetc)? *If **yes,** Med Safety to review at Medication Management Committee*	No ☒ Yes ☐
Is there unique dosing with administration (titration, guidance for determining dose, etc.)	No ☐ Yes ☒ Dose reduction to 240 mg daily if concomitantly taking cyclosporine
Is this medication on the ISMP "Do Not Crush" list?	No ☒ Yes ☐ Tablets are film-coated, but do not have special release characteristics. Manufacturer recommends swallowing tablet whole.
Does this medication require a Central Line for administration?	No ☒ Yes ☐
Is this medication infused via an infusion pump? *If **yes**, Med Safety to add to infusion pump library*	No ☐ Yes ☒
Is there a Risk Evaluation and Management Strategy (REMS) program for the medication? If so, where may healthcare providers find these criteria?	No ☒ Yes ☐
Does the medication require precautions for disposal? What kind? See EC20 Disposal of Pharmaceutical Products; EC11 Chemo Drugs-Safety Precautions for Administration	No ☒ Yes ☐
Does this medication need to be considered for auto-wasting on the MAR or another avenue for documenting waste?	No ☒ Yes ☐
Will the medication be restricted: • To a specific level of care (LOC)? See TX 24: Admission, Transfer and Discharge for Defined Levels of Care. • To a specific location? • To specific services/ providers? • To providers credentialed in deep sedation or general anesthesia? • To patients who are on the medication prior to admit?	 No ☒ Yes ☐ Unknown ☐ No ☒ Yes ☐ Unknown ☐ No ☐ Yes ☒ Unknown ☐ Restricted to Infectious Diseases services/providers No ☒ Yes ☐ Unknown ☐ No ☒ Yes ☐ Unknown ☐

References:

1. Prevymis (letermovir) [prescribing information]. Whitehouse Station, NJ: Merck & Co Inc: November 2017.
2. Cox E. NDA approval letter: Prevymis (letermovir NDA 209939 and 209940). Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/209939Orig1s000209940Orig1s000ltr.pdf. Published November 8, 2017. Accessed October 13, 2021.
3. Stoelben S, Arns W, Renders L, et al. Preemptive treatment of cytomegalovirus infection in kidney transplant recipients with letermovir: results of a phase 2a study. *Transplant Int.* 2014;27(1):77-86.
4. Kaul DR. Stoelben S, Cober E, et al. First report of successful treatment of multidrug-resistant cytomegalovirus disease with the novel anti-CMV compound AIC246. *Am J Transplant.* 2011;11(5):1079-10894.
5. Boeckh M, Murphy WJ, Peggs KS. Recent advances in cytomegalovirus: an update on pharmacologic and cellular therapies. *Bio Blood Marrow Transplant.* 2016;21:24-29.

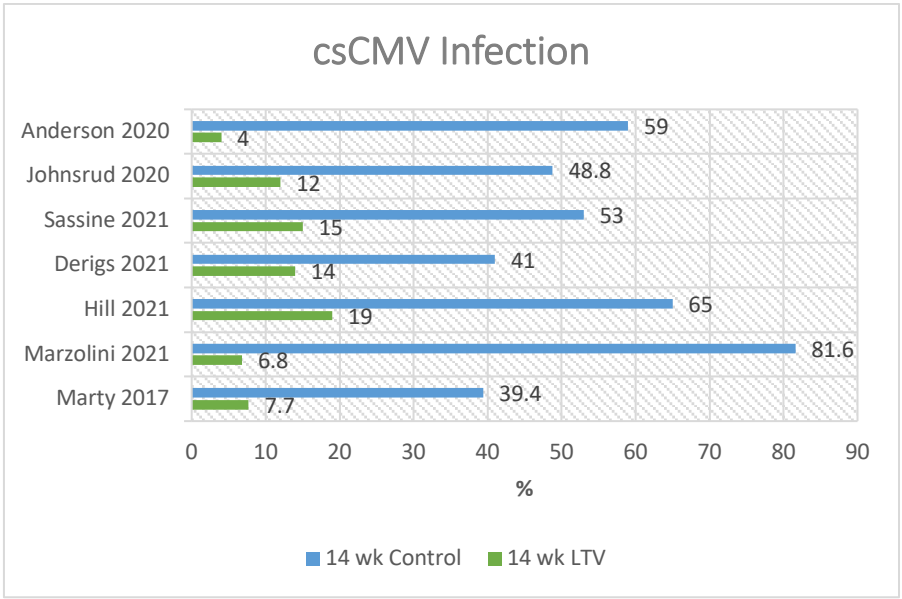
6. Dykewicz CA, Kaplan JE; Guidelines Working Group Members from CDC, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *MMWR.* 2000;49(RR 10):1-128.
7. Baden LR, Swaminathan S, Angarone M, et al. Prevention and Treatment of Cancer-Related Infections, Version 1.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2021 Jul.
8. 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. *Transplant Cell Ther.* 2021 Sept;27(9):707-719.
9. Kropeit D, McCormick D, Erb-Zohar K, et al. Pharmacokinetics and safety of the anti-human cytomegalovirus drug letermovir in subjects with hepatic impairment. *Br J Clin Pharmacol*. 2017;83(12):2678-2686.
10. Kropeit D, Scheuenpflug J, Erb-Zohar K, et al. Pharmacokinetics and safety of letermovir a novel anti-human cytomegalovirus drug, in patients with renal impairment. *Br J Clin Pharmacol.* 2017;83(9):1944-1953.
11. Kropeit D, von Richter O, Stobernack HP, et al. Pharmacokinetics and safety of letermovir coadministered with cyclosporine A or tacrolimus in healthy subjects. *Clin Pharmacol Drug Dev.* 2018;7(1):9-21.
12. Erb-Zohar K, Kropeit D, Scheuenpflug J, et al. Intravenous hydroxypropyl *β*-cyclodextrin formulation of letermovir: A phase I, randomized, single-ascending, and multiple-dose trial. *Clin Transl Sci*. 2017;10(6):487-495.
13. Wildum S, Zimmermann H, Lischka P. In vitro drug combination studies of letermovir (AIC246, MK-8228) with approved anti-human cytomegalovirus (HCMV) and anti-HIV compounds in inhibition of HCMV and HIV replication. *Antimicrob Agents Chemother.* 2015;59(6):3140-3148.
14. Goldner T, Hempel C, Ruebsamen-Schaeff H, et al. Geno- and phenotypic characterization of human cytomegalovirus mutants selected in vitro after letermovir (QIC246) exposure. *Antimicrob Agents Chemother.* 2017;58:610-613.
15. Lischka P, Hewlett G, Wunberg T, et al. In vitro and in vivo activities of the novel anticytomegalovirus compound AIC246. *Antimicrob Agents Chemother.* 2010;54(3):1290-1297.
16. Marschall M, Stamminger T, Urban A, et al. In vitro evaluation of the activities of the novel anticytomegalovirus compound AIC246 (letermovir) against herpesviruses and other human pathogenic viruses. *Antimicrob Agents Chemother.* 2012;56(2):1135-1137.
17. Chou S. Comparison of cytomegalovirus terminase gene mutations selected after exposure to three distinct inhibitor compounds. *Antimicrob Agents Chemother.* 2017;61(11):pii:e01325-17.
18. Chou S. A third component of the human cytomegalovirus terminase complex is involved in letermovir resistance. *Antiviral Res.* 2017;148:1-4.
19. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. *N Engl J Med.* 2017;377(25):2433-2444.
20. Chemaly RF, Ullman AJ, Stoelben S, et al. AIC246 Study Team. Letermovir for cytomegalovirus prophylaxis in hematopoietic-cell transplantation. *N Engl J Med.* 2014;370(19):1781-1789.
21. Clinical trials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Accessed: 10/15/2021. Available from: https://clinicaltrials.gov/.
22. Cardinal Health Order Express. Accessed October 14, 2021. https://orderexpress.cardinalhealth.com/
23. Lin A, Maloy M, Su Y, et al. Letermovir for primary and secondary cytomegalovirus prevention in allogeneic hematopoietic cell transplant recipients: Real-world experience. *Transpl Infect Dis.* 2019;21:e13187.
24. Ljungman P, Schmitt M, Marty FM, Maertens J, Chemaly RF, Kartsonis NA, Butterton JR, Wan H, Teal VL, Sarratt K, Murata Y, Leavitt RY, Badshah C. A Mortality Analysis of Letermovir Prophylaxis for Cytomegalovirus (CMV) in CMV-seropositive Recipients of Allogeneic Hematopoietic Cell Transplantation. Clin Infect Dis. 2020 Apr 10;70(8):1525-1533.

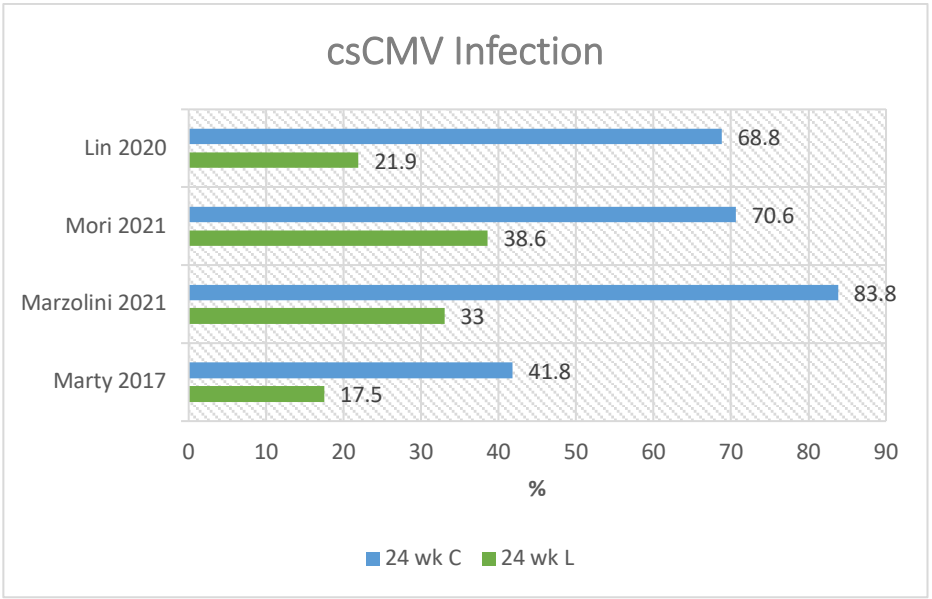
Appendix A: Literature Review on Letermovir for Primary and Secondary Prophylaxis

Author, Year	Country	Design	Use	Population, N	Population	csCMVi ~ standard def	CMV load for PET	csCMVi (LTV vs Control)
Marty, 2017	Many	P3, DB, RCT	PP	N=373 LTV N=192 PC	Allo-HCT, undetectable CMV DNA at baseline, CMV+	Y	150 copies/mL in high-risk (1st 14 wk) or 300 copies/mL in other groups and after 14 wks for all groups	24 wk: 17.5% vs 41.8% 14 wk: 7.7% vs 39.4% **this doesn't account for early discontinuation*
Marzolini, 2021	UK	RRwHC, MC (n=12)	PP	N= 110 LTV N=234 HC	Allo-HCT, CMV+	Y	ND	24 wk: 33% vs 83.8% 14 wk: 6.8% vs 81.6%
Martino, 2021	Italy	RR, MC (n=17)	PP	N=203 LTV	Allo-HCT, undetectable CMV DNA at baseline, CMV+	Y	1,000 copies/mL or 10,000 copies/ml, 2 consecutive episodes	24 wk: 18.1% 14 wk: 5.4%
Hill, 2021	US	RRwHC, SS	PP	N=21 LTV N= 40 HC (valacyclovir)	CBT, CMV+	Y	≥150 IU/mL day 1-98, ≥500 IU/mL thereafter (LTV cohort)	14 wk: 19% vs 65% 52 wk: ~61% vs 65%
Chen, 2021	US	RR, SS	PP	N=60 LTV	Allo-HCT, CMV+	Y	ND	5/60 (8.3%) required PET during prophylaxis period
Winstead, 2021	US	matched cohort, SS	PP	N= 26 LTV N=52 valGCV	SOT	N[A]	NA	CMV breakthrough 8.7% vs 13.5% (NS)
Derigs, 2021	Germany	RRwHC, SS	PP	N=80 LTV N=80 control	Allo-HCT, CMV+	Y	CMV viremia of >3,200 IU/mL	14 wk: 14% vs 41%
Styczyński, 2021	EBMT centers	RR, MC	SP	N=40 LTV	Allo-HCT	Y	NA	Breakthrough csCMVi: 4/40, 10% 60 day: 7.5%, 120 day: 10.1%
Royston, 2021 (April)	CH	Matched cohort, SS	PP	N=26 LTV N=52	Allo-HCT, CMV+	N[B]	ND	Day 180 post study inclusion: 34.6% vs 82.7%
Sassine, 2021	US	RR, SS	PP	N=123 LTV N=414 control	Allo-HCT, CMV+	Y	ND	14 wk: 15% vs 53%
Mori, 2021	Japan	RR, MC (n=8)	PP	N=114 LTV N=571 control	Allo-HCT	Y	General: ≥2 CMV antigen-positive cells per 50,000 WBC	Day 180: 38.6% vs 70.6%
Lin, 2020	US	RRwHC, SS	PP	N=32 LTV N=32 control	Allo-HCT, CMV+	Y	2 consecutive CMV viral loads >300 IU/mL, a single value of >1,000 IU/mL	Day 180: 21.9% vs 68.8%
Malagola, 2020	Italy	RRwHC, SS	PP	N=60 LTV era N=42 preLTV era	Allo-HCT	Y	Prior to 5/2019: 2 readings plasma >1,000 copies/mL, after 5/2019: 10,000 copies/mL on 2 samples, DNAemia 1,000-10,000 copies/mL in setting of additional risk factors	Day 100: 8% vs 44% Day 180: 17% vs 68% **note: not all pts in the LTV era received PP with LTV, assessment of LTV efficacy difficult in this report*
Studer, 2020	CH	RRwHC, SS	PP, SP	N= 42 LTV n=28 PP n=14 SP	Allo-HCT	N[C]	plasma CMV DNAemia >1,000 copies/ml x 2	DNAemia: Day 100 (LTV PP): 2/28, 7.1% Day 180 (LTV SP): 3/14, 21% Day 180 (HC-PET): 87/353, 24.6% **note: focus of paper was not on SP, incidence was calculated from # provided in paper*
Johnsrud, 2020	US	RRwHC, SS	PP	N=108 LTV N=637 control	Allo-HCT	Y	Viral load >400 IU/mL	Day 100: 12% vs 48.8%
Anderson, 2020	US	RRwHC, SS	PP	N=25 LTV N=52 control	Allo-HCT, CMV+	N[D]	Viral load >200 IU/mL x 2	Day 100: 4% vs 59% Day 200: 20% vs 59%
Robin, 2020	France	RR, MC (n=21)	PP, SP	N= 182 LTV n=102 PP n=80 SP	Allo-HCT	N	NA	CMV breakthrough infection or disease which required therapy: 4/80 (5.5%)
Sharma, 2020	US	RRwHC, SS	PP	N=32 LTV N=101 Valacyclovir	Allo-HCT, CMV+	Y	any initial positive PCR > 10,000 IU/ml, any repeat PCR > 5000 IU/ml after initial positive OR end-organ involvement	CMV reactivation requiring treatment: • LTV: 0/32, 0% • Valacyclovir: 15/101, 15%

Allo-HCT: allogeneic hematopoietic cell transplant, **CBT**: cord blood transplant, **CH**: Switzerland, **CI**: cumulative incidence, **CMV+**: CMV seropositive status **csCMVi** standard def: clinically significant CMV infection standard definition per Marty et al 2017 (CMV disease or CMV viremia leading to preemptive treatment), **DB**: double-blind, **HC**: historical control group, **LTV**: letermovir, **MC**: multi-center, **NA**: not applicable, **ND**: not well described, **NS**: not significant, **PC**: placebo control group, **PET**: pre-emptive treatment, **PP**: primary prophylaxis, **P3**: phase 3, **RCT**: randomized controlled trial, **RR**: retrospective review, **RRwHC**: retrospective review with historical control group, **SOT**: solid organ transplant, **SP**: secondary prophylaxis, **SS**: single center, **T**: treatment, **valGCV**: valganciclovir, **WBC**: white blood cell
csCMVi def **A**: CMV breakthrough: asymptomatic + >1,000 IU/mL or symptomatic + any viral load, **B**: csCMVi: any load >150 IU/mL and/or CMV syndrome requiring treatment, **C:** Clinically relevant CMV event: CMV DNAemia >1,000 copies/mL (x2), evidence of CMV syndrome/disease requiring PET/targeted treatment, **D**: csCMVi: DNAemia leading to PET or CMV syndrome or tissue invasive disease

1. Marzolini MAV, Mehra V, Thomson KJ, Tholouli E, Bloor AJ, Parker A, et al. Letermovir prophylaxis in T-cell depleted transplants: breakthrough and rebound infections in the post marketing setting. Blood Adv. 2021 Oct 6:bloodadvances.2021005637. doi: 10.1182/bloodadvances.2021005637.
2. Martino M, Pitino A, Gori M, Bruno B, Crescimanno A, Federico V, et al. Letermovir Prophylaxis for Cytomegalovirus Infection in Allogeneic Stem Cell Transplantation: A Real-World Experience. Front Oncol. 2021 Sep 6;11:740079. doi: 10.3389/fonc.2021.740079.
3. Hill JA, Zamora D, Xie H, Thur LA, Delaney C, Dahlberg A, Pergam SA, Leisenring WM, Boeckh M, Milano F. Delayed-onset cytomegalovirus infection is frequent after discontinuing letermovir in cord blood transplant recipients. Blood Adv. 2021 Aug 24;5(16):3113-3119. doi: 10.1182/bloodadvances.2021004362. PMID: 34402885; PMCID: PMC8405185.
4. Chen K, Arbona-Haddad E, Cheng MP, McDonnell AM, Gooptu M, Orejas JL, Timblin K, Silverman E, Al-Hamed R, Soiffer RJ, Hammond SP, Marty FM. Cytomegalovirus events in high-risk allogeneic hematopoietic-cell transplantation patients who received letermovir prophylaxis. Transpl Infect Dis. 2021 Aug;23(4):e13619. doi: 10.1111/tid.13619. Epub 2021 May 5. PMID: 33866648.
5. Winstead RJ, Kumar D, Brown A, Yakubu I, Song C, Thacker L, Gupta G. Letermovir prophylaxis in solid organ transplant-Assessing CMV breakthrough and tacrolimus drug interaction. Transpl Infect Dis. 2021 Aug;23(4):e13570. doi: 10.1111/tid.13570. Epub 2021 Feb 10. PMID: 33469975.
6. Derigs P, Radujkovic A, Schubert ML, Schnitzler P, Schöning T, Müller-Tidow C, Hegenbart U, Schönland SO, Luft T, Dreger P, Schmitt M. Letermovir prophylaxis is effective in preventing cytomegalovirus reactivation after allogeneic hematopoietic cell transplantation: single-center real-world data. Ann Hematol. 2021 Aug;100(8):2087-2093. doi: 10.1007/s00277-020-04362-2. Epub 2020 Dec 3. PMID: 33270162; PMCID: PMC8285358.
7. Styczyński J, Tridello G, Xhaard A, Medinger M, Mielke S, Taskinen M, Blijlevens N, Rodriguez MAB, Solano C, Nikolousis E, Biffi A, Groll AH, Junghanss C, Tsirigotis P, Lioure B, Šrámek J, Holler E, Galaverna F, Fagioli F, Knelange N, Wendel L, Gil L, de la Camara R, Mikulska M, Ljungman P. Use of letermovir in off-label indications: Infectious Diseases Working Party of European Society of Blood and Marrow Transplantation retrospective study. Bone Marrow Transplant. 2021 May;56(5):1171-1179. doi: 10.1038/s41409-020-01166-w. Epub 2020 Dec 7. PMID: 33288863.
8. Royston L, Royston E, Masouridi-Levrat S, Vernaz N, Chalandon Y, Van Delden C, Neofytos D. Letermovir Primary Prophylaxis in High-Risk Hematopoietic Cell Transplant Recipients: A Matched Cohort Study. Vaccines (Basel). 2021 Apr 12;9(4):372. doi: 10.3390/vaccines9040372. PMID: 33921218; PMCID: PMC8069238.
9. Sassine J, Khawaja F, Shigle TL, Handy V, Foolad F, Aitken S, Jiang Y, Champlin R, Shpall E, Rezvani K, Ariza-Heredia EJ, Chemaly RF. Refractory and Resistant Cytomegalovirus after Hematopoietic Cell Transplant in the Letermovir Primary Prophylaxis Era. Clin Infect Dis. 2021 Apr 8:ciab298. doi: 10.1093/cid/ciab298. Epub ahead of print. PMID: 33830182.
10. Mori Y, Jinnouchi F, Takenaka K, Aoki T, Kuriyama T, Kadowaki M, Odawara J, Ueno T, Kohno K, Harada T, Yoshimoto G, Takase K, Henzan H, Kato K, Ito Y, Kamimura T, Ohno Y, Ogawa R, Eto T, Nagafuji K, Akashi K, Miyamoto T. Efficacy of prophylactic letermovir for cytomegalovirus reactivation in hematopoietic cell transplantation: a multicenter real-world data. Bone Marrow Transplant. 2021 Apr;56(4):853-862. doi: 10.1038/s41409-020-01082-z. Epub 2020 Nov 2. PMID: 33139867.
11. Lin A, Flynn J, DeRespiris L, Figgins B, Griffin M, Lau C, Proli A, Devlin SM, Cho C, Tamari R, Jakubowski AA, Papadopoulos EB, Giralt SA, Perales MA, Seo SK, Shaffer B. Letermovir for Prevention of Cytomegalovirus Reactivation in Haploidentical and Mismatched Adult Donor Allogeneic Hematopoietic Cell Transplantation with Post-Transplantation Cyclophosphamide for Graft-versus-Host Disease Prophylaxis. Transplant Cell Ther. 2021 Jan;27(1):85.e1-85.e6. doi: 10.1016/j.bbmt.2020.10.009. Epub 2020 Oct 11. PMID: 33053449; PMCID: PMC8441845.
12. Malagola M, Pollara C, Polverelli N, Zollner T, Bettoni D, Gandolfi L, Gramegna D, Morello E, Turra A, Corbellini S, Signorini L, Moioli G, Bernardi S, Zanaglio C, Farina M, Testa TE, Caruso A, Russo D. Advances in CMV Management: A Single Center Real-Life Experience. Front Cell Dev Biol. 2020 Oct 27;8:534268. doi: 10.3389/fcell.2020.534268. PMID: 33195184; PMCID: PMC7652755.
13. Studer U, Khanna N, Leuzinger K, Hirsch HH, Heim D, Lengerke C, Tsakiris DA, Halter J, Gerull S, Passweg J, Medinger M, Gwerder M. Incidence of CMV Replication and the Role of Letermovir Primary/Secondary Prophylaxis in the Early Phase After Allogeneic Hematopoietic Stem Cell Transplantation - A Single Centre Study. Anticancer Res. 2020 Oct;40(10):5909-5917. doi: 10.21873/anticanres.14611. PMID: 32988922.
14. Johnsrud JJ, Nguyen IT, Domingo W, Narasimhan B, Efron B, Brown JW. Letermovir Prophylaxis Decreases Burden of Cytomegalovirus (CMV) in Patients at High Risk for CMV Disease Following Hematopoietic Cell Transplant. Biol Blood Marrow Transplant. 2020 Oct;26(10):1963-1970. doi: 10.1016/j.bbmt.2020.07.002. Epub 2020 Jul 9. PMID: 32653623.
15. Anderson A, Raja M, Vazquez N, Morris M, Komanduri K, Camargo J. Clinical "real-world" experience with letermovir for prevention of cytomegalovirus infection in allogeneic hematopoietic cell transplant recipients. Clin Transplant. 2020 Jul;34(7):e13866. doi: 10.1111/ctr.13866. Epub 2020 Apr 19. PMID: 32242979.
16. Robin C, Thiebaut A, Alain S, Sicre de Fontbrune F, Berceanu A, D'Aveni M, Ceballos P, Redjoul R, Nguyen-Quoc S, Bénard N, Pahlavan-Grumel G, Cordonnier C. Letermovir for Secondary Prophylaxis of Cytomegalovirus Infection and Disease after Allogeneic Hematopoietic Cell Transplantation: Results from the French Compassionate Program. Biol Blood Marrow Transplant. 2020 May;26(5):978-984. doi: 10.1016/j.bbmt.2020.01.027. Epub 2020 Feb 5. PMID: 32035273.
17. Sharma P, Gakhar N, MacDonald J, Abidi MZ, Benamu E, Bajrovic V, Purev E, Haverkos BM, Tobin J, Kaiser J, Chase S, Miller M, Weinberg A, Gutman JA. Letermovir prophylaxis through day 100 post transplant is safe and effective compared with alternative CMV prophylaxis strategies following adult cord blood and haploidentical cord blood transplantation. Bone Marrow Transplant. 2020 Apr;55(4):780-786. doi: 10.1038/s41409-019-0730-y. Epub 2019 Oct 29. PMID: 31664185.


csCMV Infection
Anderson 2020
Johnsrud 2020
Sassine 2021
Derigs 2021
Hill 2021
Marzolini 2021
Marty 2017
59
4
48.8
12
53
15
41
14
65
19
81.6
6.8
39.4
7.7
0
10
20
30
40
50
60
70
80
90
%
14 wk Control
14 wk LTV


csCMV Infection
Lin 2020
Mori 2021
Marzolini 2021
Marty 2017
68.8
21.9
70.6
38.6
83.8
33
41.8
17.5
0
10
20
30
40
50
60
70
80
90
%
24 wk C
24 wk L

Appendix B: Select articles on the use of letermovir for treatment of CMV

Author, Year	Country	Design	Inclusion	Patients	Regimen	Outcome	Notes
Veit, 2021	Germany	RR	Lung transplant recipients treated with LTV for 'difficult to treat CMV infection'	N=28 Out of 230 lung transplant recipients	480 mg or 240 mg PO daily	23 patients (82.1%) were responders *Responder: significant log 10 decrease of viral load after 4 weeks of therapy*	Many (n=10, 36%) of the patients had simultaneous interventions (e.g., CMV Ig, immunosuppression regimen changes).
Jorgenson, 2021	US	RR	Kidney (or kidney/pancreas) transplant recipients on LTV & valganciclovir for persistent low level CMV refractory viremia (viral loads log_{10}<3)	N=8	LTV 480 mg daily, valganciclovir 900 mg BID	Median viral load did not change significantly at 2, 4, 12 weeks. No patient cleared to negativity while on LTV.	See Table 4 for a literature summary of LTV use for treatment of CMV in SOT
Linder, 2021	US	RR, MC (n=13)	HCT or SOT, used LTV for treatment of an established CMV infection	N=47 n=27 SOT n=21 HCT	At initiation: 480 mg (87%) or 720 mg (13%). n=4 had an increase of dose during treatment. LTV monotherapy: 85%	Clinical failure: 4/47 (8.5%) Virological: <1000 IU/mL at start of LTV: 2/34 (6%) had a 1 log increase in viral load >1000 IU/mL at start of LTV, at 2-4 wks: 4/8 did not achieve a 1 log reduction, 4/10 did not have viral load <1000 IU/mL at LTV end (2 ongoing).[table 4]	Authors note LTV may be more useful in step down therapy since results with those who at viral load >1000 IU/mL had mixed results.
Styczyński, 2021	EBMT centers	RR	Off-label use of LTV	N=7 treatment	240-480mg	Treatment of CMV disease (colitis/pneumonia): 2/2 cleared infection Pre-emptive treatment: 0/5 had antiviral effect, 4/5 received second LTV course (3=good response, 1=refractory)	
Kachur, 2021	US	RR, SS	Allo-HCT, LTV for treatment of CMV infection	N=15 14 w/DNAemia, 1 w/CMV disease	480mg daily LTV monotherapy: 14/15 (CMV DNAemia).	2/15 clinical failure 3/15 late onset reactivation **Clinical failure: switch or addition of therapy, adverse effects, resistance, CMV disease development while on LTV*	Mainly in outpatients, compared those receiving LTV to a standard therapy group
Schubert, 2021	AT	RR, SS	Patients with CMV viremia/infection, LTV for compassionate use	N=9	240 mg -480 mg daily	Viral response: 7/9 (78%), 2 stopped therapy pre-maturely Viral recurrence: 1/8 (n=1 did not obtain initial viral suppression) *Response: decline of viral load to less than 200 IU/mL, CMV infection: CMV DNA >200 IU/mL*	Noted 7/9 experienced initial increase (~2.7 fold) in viral load

AT: Austria, **CH:** Switzerland, **HCT:** allogeneic hematopoietic cell transplant, **LTV**: letermovir, **MC**: multicenter, **RR**: retrospective review, **SOT**: solid organ transplant,

18. Veit T, Munker D, Barton J, Milger K, Kauke T, Meiser B, et al. Letermovir in lung transplant recipients with cytomegalovirus infection: A retrospective observational study. Am J Transplant. 2021 Oct;21(10):3449-3455. doi: 10.1111/ajt.16718. Epub 2021 Jul 3.
19. Jorgenson MR, Descourouez JL, Garg N, Parajuli S, Mandelbrot DA, Odorico JS, Saddler CM, Smith JA. The addition of adjunctive letermovir to valganciclovir for refractory cytomegalovirus viremia in kidney transplant recipients. Transpl Infect Dis. 2021 Aug;23(4):e13693. doi: 10.1111/tid.13693. Epub 2021 Jul 30. PMID: 34309158.

20. Linder KA, Kovacs C, Mullane KM, Wolfe C, Clark NM, La Hoz RM, Smith J, Kotton CN, Limaye AP, Malinis M, Hakki M, Mishkin A, Gonzalez AA, Prono MD, Ostrander D, Avery R, Kaul DR. Letermovir treatment of cytomegalovirus infection or disease in solid organ and hematopoietic cell transplant recipients. Transpl Infect Dis. 2021 Aug;23(4):e13687. doi: 10.1111/tid.13687. Epub 2021 Jul 20. PMID: 34251742.
21. Styczyński J, Tridello G, Xhaard A, Medinger M, Mielke S, Taskinen M, Blijlevens N, Rodriguez MAB, Solano C, Nikolousis E, Biffi A, Groll AH, Junghanss C, Tsirigotis P, Lioure B, Šrámek J, Holler E, Galaverna F, Fagioli F, Knelange N, Wendel L, Gil L, de la Camara R, Mikulska M, Ljungman P. Use of letermovir in off-label indications: Infectious Diseases Working Party of European Society of Blood and Marrow Transplantation retrospective study. Bone Marrow Transplant. 2021 May;56(5):1171-1179. doi: 10.1038/s41409-020-01166-w. Epub 2020 Dec 7. PMID: 33288863.
22. Kachur E, Roshdy D, Hamadeh I, Dodd B, Shahid Z. Single-center experience with use of letermovir for treatment of CMV infection in stem cell transplant recipients. Transpl Infect Dis. 2021 Apr;23(2):e13502. doi: 10.1111/tid.13502. Epub 2020 Dec 2. PMID: 33171005.
23. Schubert L, Fisecker L, Thalhammer F, Burgmann H, Steininger C. Letermovir for the compassionate therapeutic use of cytomegalovirus infection. Eur J Clin Microbiol Infect Dis. 2021 Feb;40(2):435-439. doi: 10.1007/s10096-020-03990-w. Epub 2020 Sep 11. PMID: 32914220; PMCID: PMC7817558.

Not all case reports or case series were included in this literature review. Below are some additional articles that describe >1<10 cases.

- Rho E, Näf B, Tf M, Rp W, Schachter T, von Moos S. Use of Letermovir-Valganciclovir combination as a step-down treatment after Foscarnet for Ganciclovir-resistant CMV infection in kidney transplant recipients. Clin Transplant. 2021 Jun 28. doi: 10.1111/ctr.14401. Epub ahead of print. PMID: 34181768.
- Hofmann E, Sidler D, Dahdal S, Bittel P, Suter-Riniker F, Manuel O, Walti LN, Hirzel C. Emergence of letermovir resistance in solid organ transplant recipients with ganciclovir resistant cytomegalovirus infection: A case series and review of the literature. Transpl Infect Dis. 2021 Jun;23(3):e13515. doi: 10.1111/tid.13515. Epub 2020 Dec 6. PMID: 33210830.
- Phoompoung P, Ferreira VH, Tikkanen J, Husain S, Viswabandya A, Kumar D, Humar A. Letermovir as Salvage Therapy for Cytomegalovirus Infection in Transplant Recipients. Transplantation. 2020 Feb;104(2):404-409. doi: 10.1097/TP.0000000000002785. PMID: 32000236.
- Veit T, Munker D, Kauke T, Zoller M, Michel S, Ceelen F, Schiopu S, Barton J, Arnold P, Milger K, Behr J, Kneidinger N. Letermovir for Difficult to Treat Cytomegalovirus Infection in Lung Transplant Recipients. Transplantation. 2020 Feb;104(2):410-414. doi: 10.1097/TP.0000000000002886. PMID: 31385924.
- Aryal S, Katugaha SB, Cochrane A, Brown AW, Nathan SD, Shlobin OA, Ahmad K, Marinak L, Chun J, Fregoso M, Desai S, King C. Single-center experience with use of letermovir for CMV prophylaxis or treatment in thoracic organ transplant recipients. Transpl Infect Dis. 2019 Dec;21(6):e13166. doi: 10.1111/tid.13166. Epub 2019 Sep 18. PMID: 31487755.
- Turner N, Strand A, Grewal DS, Cox G, Arif S, Baker AW, Maziarz EK, Saullo JH, Wolfe CR. Use of Letermovir as Salvage Therapy for Drug-Resistant Cytomegalovirus Retinitis. Antimicrob Agents Chemother. 2019 Feb 26;63(3):e02337-18. doi: 10.1128/AAC.02337-18. PMID: 30642941; PMCID: PMC6395918.

Appendix C: Pharmacoeconomic analyses

Author, Year	Country	Design	Perspective	Data based on	Population	Outcome	Merck PCOI
Golan, 2021	US	Post-hoc analysis of phase III trial	LTV PP, Re-hospitalizations, LOS	Marty et al, 2017	N=325 LTV N=170 PC	Standardized all cause re-hospitalization was lower at week 14 in LTV group but did not differ at wk 24, 48.	Yes
Alsumali, 2021	US, UK	Decision analytic model, Markov model	LTV PP, US Payer	Marty et al, 2017	100 hypothetical allo-HCT LTV vs no ppx	ICER at wk 24: $25,046 per QALY, considered cost-effective	Yes
Chan, 2020	CN	Decision analytic model	LTV PP, Hong Kong HCP	Marty et al, 2017	Allo-HCT on LTV 240mg vs PET	ICER: at wk 24: $30,508 per QALY Falls below 1 GDP/capita (cost-effectiveness threshold)	Yes
Restelli, 2019	Italy	Decision analytic model	LTV PP, Italian NHS	Marty et al, 2017	Allo-HCT	ICER:22,564 or 23,861 euros per QALY Cost-effective for Italian NHS	Yes

CN: China, **GDP:** gross domestic product, **HCP:** health care provider, **LOS:** length of stay, **LTV:** letermovir, **Merck PCOI:** Merck potential conflict of interest, **NHS:** national health service, **PC:** placebo control, **PET**: pre-emptive therapy, **PP**: primary prophylaxis, **PPX**: prophylaxis, **UK**: United Kingdom, **US**: United States, **QALY**: quality adjusted life years

24. Golan Y, Tang Y, Mt-Isa S, Wan H, Teal V, Badshah C, Dadwal S. Impact of Letermovir Use for Cytomegalovirus Prophylaxis on Re-Hospitalization Following Allogeneic Hematopoietic Stem Cell Transplantation: An Analysis of a Phase III Randomized Clinical Trial. Pharmacoecon Open. 2021 Sep;5(3):469-473. doi: 10.1007/s41669-021-00264-9. Epub 2021 Apr 19. PMID: 33871830; PMCID: PMC8333192
25. Alsumali A, Chemaly RF, Graham J, Jiang Y, Merchant S, Miles L, Schelfhout J, Yang J, Tang Y. Cost-effectiveness analysis of cytomegalovirus prophylaxis in allogeneic hematopoietic cell transplant recipients from a US payer perspective. J Med Virol. 2021 Jun;93(6):3786-3794. doi: 10.1002/jmv.26462. Epub 2020 Oct 5. PMID: 32844453.
26. Chan TS, Cheng SS, Chen WT, Hsu DC, Chau RW, Kang SH, Alsumali A, Kwong YL. Cost-effectiveness of letermovir as cytomegalovirus prophylaxis in adult recipients of allogeneic hematopoietic stem cell transplantation in Hong Kong. J Med Econ. 2020 Dec;23(12):1485-1492. doi: 10.1080/13696998.2020.1843321. Epub 2020 Nov 12. PMID: 33155494.
27. Restelli U, Croce D, Pacelli V, Ciceri F, Girmenia C. Cost-effectiveness analysis of the use of letermovir for the prophylaxis of cytomegalovirus in adult cytomegalovirus seropositive recipients undergoing allogenic hematopoietic stem cell transplantation in Italy. Infect Drug Resist. 2019 May 8;12:1127-1138. doi: 10.2147/IDR.S196282. PMID: 31190905; PMCID: PMC6512572.