MONTEFIORE MEDICAL CENTER
The University Hospital for the

Albert Einstein College of Medicine

MANUAL CODE:

SUBJECT: Clinical guidelines for the use of letermovir

OWNER: Infectious Disease Consultative Service and Bone Marrow Transplant Program

EFFECTIVE: April 12, 2018

Purpose:
To provide a clinical guideline and institutional policy regarding the use of letermovir for cytomegalovirus prophylaxis (CMV) in allogeneic bone marrow transplant (BMT) recipients.

Mechanism of action:
Letermovir acts by inhibiting the viral terminase complex of CMV. It has no activity against HSV1, HSV2, VZV or other viruses

- Based on the lack of activity against other viruses, patients should remain on acyclovir or valacyclovir prophylaxis in addition to letermovir therapy

Eligibility:
All CMV IgG positive patients without evidence of CMV viremia who are Day +5 to Day +28 post-allogeneic stem cell transplantation

Prior to initiation:
The following steps must be performed prior to initiation of letermovir:

- Check patients insurance coverage upon admission and confirm coverage of letermovir as an outpatient
- Send CMV PCR on Day +2 or 3 (results will need to be available by Day +5)
- Place order for Infectious Diseases consultation for approval prior to Day +5

****Patients with active CMV viremia or who are unable to obtain outpatient insurance coverage should NOT be started on letermovir****

Regimen:
Patients who meet the above criteria should begin letermovir on Day +5 as follows:

- Standard dose/administration: letermovir 480mg PO q24h (give 240mg PO q24h if patient is on cyclosporine)
    - No renal adjustment required for CrCl ≥ 10ml/min
    - No dosing recommendations have been made for patients with CrCl ≤10ml/min or on hemodialysis
- If unable to tolerate PO, can administer letermovir 480mg IV q24h (give 240mg IV if patient is on cyclosporine)
    - Accumulation of the IV vehicle hydroxypropyl betadex (known as cyclodextran) can occur in patients with CrCl < 50ml/min receiving letermovir IV. Close monitoring of serum creatinine is recommended. Switch to PO letermovir as soon as patient is able to take PO medication.

Drug interactions:

Letermovir is a substrate of organic anion-transporting polypeptide 1B1/3 (OATP1B1/3) transporters and it also is an inhibitor of OATP1B1/3 transporters. Letermovir is also a moderate inhibitor and inducer of CYP3A, 2C9, 2C19, etc. The magnitude of CYP3A and OATP1B1/3-mediated drug interactions on co-administered drugs may be different when letermovir is co-administered with cyclosporine.

Concomitant Drug/Class	Effect on Concentration	Clinical Comment
pimozide	↑ pimozide	Increase QT prolongation and torsades de pointes
ergot alkaloids (ergotamine, dihydroergotamine)	↑ ergot alkaloids	Ergotism
amiodarone	↑ amiodarone	Close clinical monitoring for adverse events related to amiodarone. When letermovir is co-administered with cyclosporine, use of amiodarone is not recommended.
glyburide, repaglinide, rosiglitazone	↑ glyburide ↑ repaglinide ↑ rosiglitazone	Frequent monitoring glucose When letermovir is co-administered with cyclosporine, use of repaglinide is not recommended.
voriconazole	↓ voriconazole	Monitoring reduced effectiveness of voriconazole, monitor voriconazole level
atorvastatin	↑ atorvastatin	Dose of atorvastatin should NOT exceed 20mg daily When letermovir is co-administered with

		cyclosporine, use of atorvastatin is not recommended.
simvastatin **pitavastatin**	↑ simvastatin ↑ pivastatin	Concomitant use with letermovir is NOT recommended. When letermovir is co-administered with cyclosporine, use of simvastatin or pitavastatin is contraindicated.
fluvastatin **lovastatin** **pravastatin** **rosuvastatin**	↑ fluvastatin ↑ lovastatin ↑ pravastatin ↑ rosuvastatin	A statin dosage reduction maybe necessary. When letermovir is co-administered with cyclosporine, use of lovastatin is not recommended.
cyclosporine	↑ cyclosporine ↑ letermovir	Concomitant use increases concentrations of both letermovir and cyclosporine. Decrease letermovir to 240mg once daily. Monitor cyclosporine level. Frequent monitoring of cyclosporine blood level.
sirolimus **tacrolimus**	↑ sirolimus ↑ tacrolimus	Monitor sirolimus and tacrolimus level
omeprazole **pantoprazole**	↓ omeprazole ↓ pantoprazole	Clinical monitoring and dose adjustment may be needed
rifampin	↓ letermovir	Co-administration of letermovir and rifampin is not recommended
phenytoin **warfarin**	↓ phenytoin ↓ warfarin	Phenytoin: monitoring phenytoin concentrations Warfarin: monitoring INR
fentanyl **midazolam** **quinidine**	↑ [CYP 3A substrate]	Dose adjustment of CYP 3A substrates maybe needed. Fentanyl, midazolam: monitoring respiratory depression and prolonged sedation Quinidine: monitoring ventricular arrhythmia and hypotension
aprepitant	may ↑ aprepitant	Avoid combination of letermovir and aprepitant

Duration:

- Letermovir should be continued from Day +5 through Day +100

Monitoring:

- CMV PCR must be monitored weekly

- Mutations of genes UL 56, UL 89 and UL51 confer resistance to letermovir and have been reported from the phase 3 trial and in vitro studies.
- If patients develop CMV viremia on letermovir, letermovir should be discontinued immediately and the patient should begin treatment as per the Bone Marrow Transplant and Immunocompromised Infectious Diseases services
- Cross resistance is not likely with other anti-CMV agents

Other patients:

There is no data supporting the use of letermovir in patients who do not meet the above criteria. In these cases, the decision to start letermovir should be made on a case by case basis in consultation with the Immunocompromised Infectious Diseases Services and/or Antimicrobial Stewardship Program.

References:

1. Marty FM, Ljungman P, Chemaly RF et al. Letermovir prophylaxis for Cytomegalovirus in hematopoietic-stem cell transplantation. *The New England Journal of Medicine* 2017; 377:2433-2444
2. Merck & Co, Inc. PREVYMIS (LETERMOVIR) tablets and injection prescribing information. 2017 Nov
3. Chou S. Rapid in vitro evolution of human cytomegalovirus UL56 mutations that confer letermovir resistance. Antimicrob Agents Chemother 2015; 59 (10):6588-6593.