Letermovir in Solid Organ Transplants v5

Oct 2018

Background:

Letermovir (Prevymis®, Merck Canada Inc.) was launched in Canada in Dec 2017, and marketed for CMV prophylaxis for allogeneic hematopoietic stem cell transplant HSCT (bone marrow transplant) based a double-blind, randomized placebo-controlled trial (Study P001, n=570). It's novel mechanism of action, inhibition of CMV DNA terminase complex results in the inhibition of viral maturation.[1] Letermovir spectrum of activity is specific to human CMV with no activity against HSV or VZV. It's favourable side effect profile suggests it does not have the same bone marrow suppressive activity as ganclovir/valganciclovir, nor the renal toxicity of foscarnet/cidofovir.

The recent CADTH (Canadian Agency for Drugs and Technologies in Health) review has recommended Provincial funding agencies consider reimbursement for prophylaxis of CMV for adult CMV R+ recipients for HSCT[2]. BC Pharmacare is currently reviewing letermovir for special authority support for HSCT CMV prophylaxis based on the CADTH recommendation. The report noted that despite the lack of published evidence, letermovir may be considered for off-label indications such as recurrent and/or resistant CMV, pre-emptive therapy and treatment for viremic patients.[2]

Evidence for letermovir use in solid organ transplants (SOT):

The evidence for letermovir use in solid organ transplants is very limited. The renal transplant group in Vancouver is going to be participating in a randomized controlled trial of letermovir vs valganciclovir for prophylaxis of CMV in high risk D+/R- kidney transplant recipients (NCT3443869). The results of this trial will help expand the prophylaxis indication to include solid organ transplants. Valganciclovir continues to be the drug of choice for both prophylaxis and treatment for ambulatory patients.[3]

There has been a Phase II study looking at using letermovir for pre-emptive therapy for CMV viremia, however, the doses used in that study were much lower than those currently used for the prophylaxis indication.[4] Letermovir is currently not approved for pre-emptive therapy or treatment of CMV disease.

Recommendation:

Letermovir's novel mechanism of action and favourable side effect profile may offer advantages over traditional antivirals. However, due to the lack of published evidence on letermovir for SOT (prophylaxis or treatment), it's low genetic barrier for resistance and it's high cost, BC Transplant Drug Strategy Advisory Committee supports the addition of letermovir to the BC Transplant Drug Formulary on a ***restricted basis.***

Clinicians are required to consult the Transplant Infectious Disease specialist to review therapeutic options for CMV prophylaxis/treatment. Letermovir is ***reserved for CMV primary/secondary prophylaxis*** (CMV viral load less than 35 IU prior to starting letermovir)

- CMV resistance to ganciclovir/valganciclovir
- Allergy to ganciclovir or valganciclovir
- Significant neutropenia (persistently less than 0.5 10^9/L) prior to CMV antiviral therapy despite filgrastim/G-CSF support and unable to reduce immunosuppression

If CMV viral load is above 35 IU/mL while on letermovir prophylaxis, discontinue letermovir and treat viremia using alternate CMV antivirals. Due to letermovir's lack of activity against HSV/VZV, additional antiviral therapy may be necessary.

An annual report will be presented to the Drug Strategy Advisory Committee summarizing the clinical criteria for usage and budget impact.

References:

[1] Infection and Drug Resistance 2015; 8: 269-277

[2] CADTH (Canadian Agency for Drugs and Technologies in Health) Drug Reimbursement Recommendation June 2018

[3] Transplantation. 2018 Jun;102(6):900-931

[4] Transpl Int. 2014 Jan;27(1):77-86

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Letermovir Authorization Request

1. After ID consultation, provider/clinic to complete form and forward prescription to BC Transplant Pharmacy.

2. BC Transplant Pharmacy to fax form to BC Transplant office
Fax: 604-877-2111

3. Please wait for authorization prior to dispensing

BCT ID:

Name:

PHN:

Organ group: ☐ Heart ☐ Kidney ☐ Liver ☐ Lung ☐ Pancreas/Islet Requesting clinic: _____

Transplant Infectious Disease Consult: ☐ Yes ☐ No

Indication(s) for letermovir prophylaxis:

☐ CMV resistance to ganciclovir or valganciclovir
☐ Allergy to ganciclovir or valganciclovir
☐ Significant neutropenia (neutrophils persistently <0.5) prior to CMV antiviral therapy despite filgrastim/G-CSF support and unable to reduce immunosuppression
☐ Other: (with Transplant ID approval) _____

NOTE: If CMV VL > 35 IU/mL, discontinue letermovir and treat viremia using alternate CMV antivirals. Additional HSV/VZV therapy may necessary as letermovir lacks of herpes virus activity.

Notes: _____
_____

Prescription: Letermovir (Prevymis®) - available in 28 day blister pack
- Ensure BCT has authorized prior to dispensing
- Dispense maximum 4 week supply at a time; maximum 24 week total course authorization*

☐ first course ☐ subsequent course

☐ letermovir 480 mg PO daily for
☐ 4 weeks ☐ 12 weeks ☐ 24 weeks (max) ☐ _____ weeks

If patient is on cyclosporine:
☐ letermovir 240 mg PO daily for
☐ 4 weeks ☐ 12 weeks ☐ 24 weeks (max) ☐ _____ weeks

Pharmacy:
☐ VGH ☐ SPH
☐ BCCH ☐ RJH (Victoria)

☐ Abbotsford ☐ Nanaimo
☐ Langley ☐ Kamloops
☐ Kelowna ☐ Penticton
☐ Prince George ☐ Trail
☐ Surrey ☐ Other _____

*If a patient requires extended durations greater than 6 months or additional courses, a separate application needs to be submitted.

Prescriber signature | Print Name | College ID | Date

BCT Authorization: ☐ Yes ☐ No Date _____ Notes: _____

Please fax completed form to BC Transplant office: Fax: 604-877-2111 Attn: Pharmacy Coordinator