

Letermovir

Approved indication: cytomegalovirus prophylaxis

Prevymis (Merck Sharp and Dohme)

240 mg film-coated tablets

Australian Medicines Handbook section 5.3, Antivirals

Cytomegalovirus can cause opportunistic infections in patients who are immunocompromised. For example, after haematopoietic stem cell transplantation cytomegalovirus infection can lead to pneumonia or encephalitis. As the consequences of infection can be fatal, prophylaxis has been considered, however antiviral drugs such as ganciclovir can be toxic in these patients. Some specialist centres give pre-emptive treatment if there is laboratory evidence of infection even if there are no symptoms.

Letermovir is an inhibitor of cytomegalovirus terminase. This inhibition interferes with the maturation of viral DNA.

The bioavailability of the letermovir tablets in patients who have had a stem cell transplant is influenced by ciclosporin. Lower doses are used in patients taking ciclosporin as the bioavailability is 85% compared with 35% in those taking letermovir alone. This is because ciclosporin is an inhibitor of organic ion transporters. Although little of the letermovir molecule is metabolised, it can inhibit cytochrome P450 3A. This creates the potential for interactions with drugs such as midazolam. Although not all drugs have been studied, other commonly used medicines that may interact with letermovir include statins, proton pump inhibitors, phenytoin and warfarin. Co-administration with ergot alkaloids, pimozide, and ciclosporin with simvastatin is contraindicated.

Most of the dose of letermovir is excreted in the faeces. It should not be used in severe hepatic impairment, or moderate impairment if the patient also has moderate or severe renal impairment.

The main trial of letermovir prophylaxis studied patients having allogeneic haematopoietic cell transplantation who were seropositive for cytomegalovirus but had no detectable viral DNA. Oral or intravenous letermovir was given to 373 patients and 192 were given placebo. Prophylaxis began up to 28 days after the transplant. It continued up to 14 weeks after the transplant. A daily dose of letermovir 480 mg was used, apart from patients taking ciclosporin who used 240 mg daily.

By 24 weeks after transplantation 60.6% of the placebo group had developed a clinically significant cytomegalovirus infection. In the letermovir group 37.5% developed an infection. Pre-emptive therapy was started in 16% of the letermovir group and 40% of the placebo group. All-cause mortality was 10.2% with letermovir and 15.9% with placebo.¹

Treatment was discontinued before 24 weeks by 1.8% of the letermovir group and 0.6% of the placebo group because of adverse events. The frequency of adverse events was similar for letermovir and placebo. Cardiac adverse events, such as tachycardia and atrial fibrillation, were more frequent with letermovir than placebo (13% vs 6%). Peripheral oedema was also more frequent (14.5% vs 9.4%).¹

The optimum use of letermovir requires more investigation. It is indicated for up to 100 days of prophylaxis, but after that time the infection rate rises. By 48 weeks the difference in all-cause mortality between letermovir and placebo was no longer statistically significant (20.9% vs 25.5%). The virus can also develop resistance to letermovir.¹

T manufacturer provided the product information

REFERENCE

1. Marty FM, Ljungman P, Chemaly RF, Maertens J, Dadwal SS, Duarte RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. *N Engl J Med* 2017;377:2433-44. <https://doi.org/10.1056/NEJMoa1706640>

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The Transparency Score is explained in [New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27](#).

At the time the comment was prepared, information about this drug was available on the websites of the [Food and Drug Administration](#) in the USA, and the [European Medicines Agency](#).