# Health Technology Briefing
# April 2023

# Letermovir for preventing cytomegalovirus in children and adolescents following allogeneic haematopoietic stem cell transplant

| Company/Developer | Merck Sharp & Dohme Ltd |
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☐ New Active Substance ☒ Significant Licence Extension (SLE)

| NIHRIO ID: 27704 | NICE ID: 11868 | UKPS ID: 666273 |
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## Licensing and Market Availability Plans

In phase II clinical development.

## Summary

Letermovir is being developed for the prevention of cytomegalovirus (CMV) in children and adolescents following allogeneic haematopoietic stem cell transplant (HSCT). CMV is a common virus that can cause mild infection. Most people get infected at some stage during their lifetime but are very often unaware of it. After infection, the virus remains in the body in a 'latent' (inactive) state and only becomes active again if the body's immunity, specifically its cell-mediated immunity, is weakened. CMV disease in patients with impaired cell-mediated immunity such as HSCT patients is long-term, debilitating, and life-threatening because of the complications it causes, such as inflammation of the lungs, liver, and the digestive tract. Prevention of CMV infection/disease in children after transplantation has been challenged by the limited number of available antivirals and side effects associated with currently available products.

Letermovir administered orally or intravenously is thought to block the action of an enzyme in the virus called 'terminase', which is involved in packaging the DNA strands to fit within the protein shells of the virus. By blocking the enzyme, letermovir is expected to prevent the DNA in the virus from reaching maturity, thereby killing the virus. If licensed, letermovir will offer an additional option for the prevention of CMV in children following allogeneic HSCT who currently have few well-tolerated and effective treatment options.

## Proposed Indication

Prevention of cytomegalovirus (CMV) infection and/or disease following allogeneic haematopoietic stem cell transplant (HSCT) in children and adolescents aged less than 18 years.[1]

## Technology

### Description

Letermovir (Prevymis) is an antiviral. It inhibits the CMV DNA terminase complex which is required for cleavage and packaging of viral progeny DNA. Letermovir affects the formation of proper unit length genomes and interferes with virion maturation.[2] During replication, CMVs have their DNA packaged into small protein shells. Letermovir is thought to block the action of an enzyme in the virus called 'terminase', which is involved in cleaving the DNA strands to fit within the shells. By blocking the enzyme, Letermovir is expected to prevent the DNA in the virus from reaching maturity, thereby killing the virus.[3]

Letermovir is in phase II clinical development for the prevention of CMV in paediatrics following allogeneic HSCT. In the Phase II clinical trial (NCT03940586), participants receive Letermovir administered as oral granules, oral tablet or intravenously within 28 days post-transplant, once daily through week 14 (approximately 100 days). Dosing vary based on age, weight, and whether participant takes cyclosporin A as a concomitant medication.[1]

### Key Innovation

Transplant recipients are at risk for CMV infection and associated morbidity and mortality.[4] Since the 90s, at least four antiviral medicinal products targeting the DNA polymerase complex have been developed for the prevention and treatment of Human cytomegalovirus(HCMV) infections in transplant recipients.[5] Side effects associated with these antiviral products include myelosuppression, nephrotoxicity and electrolyte imbalance.[4]

Letermovir is a first in class, highly potent, CMV-specific terminase enzyme inhibitor which inhibits CMV replication by binding to components of the terminase complex (UL51, UL56, or both). Since there is no human analogue of the CMV terminase complex, no human toxicity is predicted. In a phase 3 randomised, double blind placebo-controlled trial of CMV-seropositive HSCT recipients, letermovir prophylaxis significantly reduced the risk of clinically significant CMV infection and was not associated with myelosuppression.[4] If licensed, letermovir with will offer an additional prophylactic option for paediatric patients following HSCT who currently have few well-tolerated and effective treatment options.

### Regulatory & Development Status

Letermovir currently has Marketing Authorisation in the UK/EU for the prophylaxis of CMV reactivation and disease in CMV-seropositive adults following an allogeneic HSCT.[2]

Letermovir is also in phase II/ III clinical development for:[6]

- CMV prophylaxis after Lung Transplant.
- CMV reactivation prophylaxis in Leukaemia.
- CMV reactivation prophylaxis in Lymphoma.
- Congenital CMV
- CMV reactivation prophylaxis after heart transplant

Letermovir was awarded an orphan designation in the EU in 2011 for the prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity.[3]

## Patient Group

### Disease Area and Clinical Need

CMV is a common virus that usually only causes mild infection such as a sore throat. Most people get infected at some stage during their lifetime but are very often unaware of it. After infection, the virus usually remains in the body in a 'latent' (inactive) state and only becomes active if the body's immunity, specifically its cell-mediated immunity, is weakened. CMV infection in patients with impaired cell-mediated immunity is long-term debilitating and life-threatening because of the complications it causes, such as inflammation of the eyes, lungs, liver and digestive tract, as well as reduced survival of transplanted organs or tissues in transplant patients.[3] HSCT is a procedure in which a patient receives healthy blood-forming cells (stem cells) from a donor to replace their own stem cells that have been destroyed by treatment with radiation or high doses of chemotherapy.[7]

CMV infection remains a critical cause of mortality after allogeneic HSCT, despite improvement by pre-emptive antivirus treatment. A retrospective study to determine the risk factors of cytomegalovirus infection and evaluation of cytomegalovirus-specific cytotoxic T lymphocytes (CMV-CTL) in children who underwent allogeneic HSCT showed a significantly poor 5-year overall survival in children infected with CMV compared to the non-CMV group (87.3% vs 94.6%)[8] There were 320 allogeneic HSCT's for paediatric patients in the UK and Republic of Ireland in 2018.[9] In England2021-22, there were 446 finished consultant episodes (FCE) and 262 admissions for Cytomegaloviral disease, unspecified (ICD-10 code 25.9) which resulted in 2,553 FCE bed days and 59 day cases.[10]

### Recommended Treatment Options

There are currently no NICE recommendations for preventing CMV disease after an allogeneic stem cell transplant in children.

Ganciclovir is indicated for the prevention of cytomegalovirus disease as a pre-emptive therapy in children aged 12-17 years with drug-induced immunosuppression; and as a universal prophylaxis in children and neonates with drug-induced immunosuppression.[11]

Valganciclovir is indicated for the prevention of cytomegalovirus disease in neonates and children following solid organ transplantation from a cytomegalovirus positive donor.[12]

Foscarnet sodium is indicated for the induction and maintenance therapy of children with Cytomegalovirus disease.[13]

## Clinical Trial Information

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| Trial | **MK-8228-030;** NCT03940586, 2018-001326-25; A Phase 2b Open-label, Single-arm Study to Evaluate Pharmacokinetics, Efficacy, Safety and Tolerability |

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| | of Letermovir in Paediatric Participants From Birth to Less Than 18 Years of Age at Risk of Developing CMV Infection and/or Disease Following Allogeneic Haematopoietic Stem Cell Transplantation (HSCT).<br><br>**Phase II** - Active, not recruiting<br><br>**Locations**: 4 EU countries, USA, and other countries<br><br>**Primary completion date**: January 2023 |
| Trial Design | Single group assignment, open-label |
| Population | N=65 (actual); Subjects at risk of developing Cytomegalovirus infection/disease following Haematopoietic Stem Cell Transplantation (HSTC); aged 0 to 17 years old |
| Intervention(s) | • Letermovir oral granules<br>• Letermovir tablet<br>• Letermovir IV<br><br>Administered based on age, weight and whether participants take cyclosporin A as a concomitant medication. |
| Comparator(s) | No comparator |
| Outcome(s) | **Primary outcome measures:**<br>• Area under the concentration-time curve of plasma letermovir for oral formulation [Time Frame: Day 7: Pre-dose, 1, 2.5, 8 and 24 hours post-dose]<br>• Maximal concentration of plasma letermovir for oral formulation [Time Frame: Day 7: Pre-dose, 1, 2.5, 8, and 24 hours post-dose]<br>• Minimum concentration of plasma letermovir observed before next dose for oral formulation [ Time Frame: Day 7: Pre-dose]<br>• Area under the concentration-time curve of plasma letermovir for intravenous formulation [Time Frame: After 5 consecutive days of administration of intravenous formulation: Pre-dose, 1, 2.5, 8, and 24 hours post-dose (up to 14 weeks)]<br>• Concentration at the end of infusion of plasma letermovir for IV formulation [Time Frame: After 5 consecutive days of administration of IV formulation: 1 hour post-dose (up to 14 weeks)]<br>• Minimum concentration of plasma letermovir observed before next dose for IV formulation [Time Frame: After 5 consecutive days of administration of IV formulation: Pre-dose (up to 14 weeks)]<br>• Minimum concentration of plasma letermovir observed before next dose during sparse PK for oral formulation [Time Frame: Pre-dose on Weeks 2, 4, 6, 8, 12, 14]<br>• Minimum concentration of plasma letermovir observed before next dose during sparse PK for IV formulation [Time Frame: Pre-dose on Weeks 2, 4, 6, 8, 12, 14] |

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| Results (efficacy) | The proportion of adolescent patients receiving letermovir with clinically significant CMV infection (CMV disease/pre-emptive treatment for CMV viremia) through week 24 post-HSCT was similar (24%) to that for adults receiving letermovir in the pivotal Phase 3 study (37.5%).[14] |
| Results (safety) | No major safety concerns were reported for adolescent patients receiving letermovir, similar to the adult letermovir safety profile.[14] |

## Estimated Cost

Letermovir is marketed in the UK as oral tablets. A pack of 28 x 240mg tablets cost £3723.16.[15]

## Relevant Guidance

### NICE Guidance

No relevant guidance identified.

### NHS England (Policy/Commissioning) Guidance

- NHS England. Haematopoietic Stem Cell Transplantation (HSTC) All Ages.B04/P/a. July 2021.

### Other Guidance

- European Conference on Infections in Leukaemia (ECIL 7). Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7). 2019.[16]
- Management of cytomegalovirus infection in haemopoietic stem cell transplantation. 2013.[17]

## Additional Information

## References

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