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Health Technology Briefing
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Letermovir for preventing cytomegalovirus disease in kidney transplant patients

Company/Developer	Merck Sharp & Dohme Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 24090	NICE TSID: 10413	UKPS ID: 654849

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Letermovir is in clinical development for adult patients who have received a kidney transplant and are at risk of developing cytomegalovirus disease (CMV). CMV is normally a mild infection that causes flu-like symptoms but can be life-threatening in certain groups. Once infected with CMV, the virus stays in the body throughout a person's life with no symptoms. However, it can become reactivated when a person's immune system is compromised. Patients who receive an organ transplant take immunosuppressive medication to stop their immune system from rejecting the transplanted organ. This immunosuppressive medication can reactivate CMV, often leading to severe complications (such as pneumonia and swelling of the brain), or death in transplant recipients.

Letermovir works by stopping the CMV virus from replicating within the body, reducing the likelihood of it reactivating. Letermovir is administered orally once daily with cyclosporin A, and an oral dose of acyclovir will also be given every 12 hours. Currently, there are no medicinal products recommended by NICE for the prevention (prophylaxis) of CMV infection following kidney transplant. These patients often receive anti-viral treatments, however this can result in serious side effects. If licensed, letermovir with acyclovir would offer a new prophylactic option for adult patients undergoing a kidney transplant.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

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Proposed Indication

The prevention of cytomegalovirus (CMV) in adult patients receiving a kidney transplant.[1]

Technology

Description

Letermovir (Prevymis, MK-8228) is a member of a new class of non-nucleoside CMV inhibitors (3,4 dihydro-quinazolines) and inhibits viral replication by targeting the viral terminase complex.[2] Successful viral replication by CMV requires cleavage and repackaging of viral DNA, which is performed by the viral terminase complexes targeted by letermovir. This prevents CMV viral replication and therefore acts as a potent prophylaxis.[3,4]

Letermovir with acyclovir is in clinical development for the prevention of CMV disease in adult kidney transplant recipients. In the phase II clinical trial (NCT03443869), participants receive 480mg letermovir (or 240mg when co-administered with cyclosporin A) administered via oral administration once daily for 28 weeks, in addition to an oral dose of acyclovir (ACV) every 12 hours.[1]

Key Innovation

Antiviral drugs are the mainstay for the prevention of CMV infection and disease, most commonly valganciclovir. However, valganciclovir is a potential teratogen and carcinogen, and its use is often associated with adverse drug reactions, most notably leukopenia and neutropenia. Additionally, widespread use has led to emergence of antiviral resistance.[5,6,7] Therefore, there remains an unmet need to develop additional CMV prophylaxis agents for patients undergoing kidney transplant that result in less toxicity.[4] Letermovir is a novel CMV viral terminase inhibitor drug, which is approved for CMV prophylaxis in allogeneic HSCT recipients. It has a distinct mechanism targeting the terminase complex, resulting in less cross-resistance with other antiviral drugs, and has a favourable pharmacokinetic and tolerability profile.[3,7]

If licensed, letermovir with acyclovir will offer an additional prophylactic option for kidney transplant recipients who are seronegative for CMV and currently have few well-tolerated and effective treatment options.

Regulatory & Development Status

Letermovir currently has Marketing Authorisation in the EU/UK for the prevention of CMV reactivation and disease in recipients of an allogenic haematopoietic stem cell transplant who are seropositive for the human CMV.[8]

Letermovir is in phase III/ II clinical development for:[9]

- Prevention of CMV disease in paediatric patients who have undergone allogeneic haematopoietic stem cell transplantation
- Prevention of CMV disease in lung transplant recipients
- Leukaemia
- Lymphoma

Letermovir was awarded fast track status by the US FDA for the inhibition of CMV in August 2011.[10]

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Patient Group

Disease Area and Clinical Need

Cytomegalovirus (CMV) is a common viral infection that is carried by 50-80% of the population that usually only causes mild flu-like symptoms, with some people not realising they've been infected. Infection with CMV can occur through sexual contact or contact with any body fluids such as blood or breast milk.[2,11] CMV is usually controlled by the immune system but can be life-threatening in babies or immunocompromised patients such as those on immunosuppressants due to organ transplant. CMV disease can occur in immunocompromised patients and can have flu-like symptoms (common in non-immunocompromised patients), but then develop into more severe symptoms such as pneumonia, hepatitis, encephalitis, retinitis, nephritis, myocarditis and pancreatitis, increasing mortality risk. Kidney transplants are used to reduce mortality associated with length of time on dialysis of end-stage kidney disease patients but one of the most frequent causes of organ rejection is CMV infection.[12]

In the UK (2020-21), 2,287 received a kidney transplant from either a living or a deceased donor, with 3,408 patients waiting for a transplant.[13] Approximately 8% of renal transplants can be expected to experience symptomatic CMV infection.[14] In England (2020-21), there were 384 finished consultant episodes (FCE) for CMV disease (ICD-10 code: B25.9) with 251 hospital admissions that resulted in 2,448 FCE bed days and 52 day cases.[15]

Recommended Treatment Options

There are currently no NICE recommended CMV prophylaxis options for kidney transplant recipients but the British Transplant Society recommends that all renal transplant recipients should receive prophylaxis against primary infection and recommend the use of oral valganciclovir.[5]

Clinical Trial Information

Trial	NCT03443869, 2017-001055-30; A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Study to Evaluate the Efficacy and Safety of MK-8228 (Letermovir) Versus Valganciclovir for the Prevention of Human Cytomegalovirus (CMV) Disease in Adult Kidney Transplant Recipients **Phase 3** – Complete **Location(s):** 8 EU countries, UK, USA, Canada, and other countries **Study completion date:** April 2022
Trial Design	Randomised, parallel assignment, double-blind, active comparator controlled
Population	N= 601; Subjects that anticipate receiving or are up to 7 days post-transplant of a kidney from a CMV IgG seropositive (D+) donor and have negative serostatus (D-) for CMV; aged 18 years and older.
Intervention(s)	Letermovir (LET) oral tablet, 480mg (or 240 mg when co-administered with cyclosporin A) once daily for 28 weeks; placebo to Valganciclovir (VGCV) tablet orally once daily; and 400 mg capsule of ACV orally every 12 hours for 28 weeks
Comparator(s)	900 mg VGCV tablet orally, once daily; placebo to LET tablet orally once daily; and placebo to ACV orally every 12 hours for 28 weeks
Outcome(s)	Primary Outcome Measure: CMV disease 52 weeks [Time frame: Up to 52 weeks]

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	Percentage of participants with adjudicated CMV disease through 52 weeks post-transplant See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The hospital indicative price is £3,723.16 for a pack of 28 240mg tablets.[16,17]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Maribavir for treating refractory or resistant cytomegalovirus infection after transplant (ID3900) (GID-TA10792). Expected January 2023.
- NICE technology appraisal. Immunosuppressive therapy for kidney transplant in adults (TA481). October 2017.
- NICE quality standard. Renal replacement therapy services for adults (QS72). November 2014.
- NICE guideline. Renal replacement therapy and conservative management (NG107). October 2018.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Adult Kidney Transplant Service. A07/S/a.

Other Guidance

- American Society of Transplantation Infectious Diseases Community of Practice. Cytomegalovirus in solid organ transplantation recipients: Guidelines. 2019.[18]
- Transplant Society International CMV Consensus Group. The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. 2018.[19]
- British Transplant Society. The prevention and management of CMV disease after solid organ transplantation. 2016.[5]

Additional Information

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