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HEALTH TECHNOLOGY BRIEFING NOVEMBER 2020

Maribavir for cytomegalovirus infections after transplant

NIHRIO ID	2631	**NICE ID**	10163
Developer/Company	Takeda UK Ltd	**UKPS ID**	656065

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Maribavir is being developed for the treatment of cytomegalovirus (CMV) infections and the first indication expected for maribavir is for patients that are clinically refractory and/or genetically resistant to ganciclovir (GCV), valganciclovir (VGCV), cidofovir (CDV) and foscarnet (FOS). CMV is a common virus that usually only causes mild infection. In people with weakened immunity, such as transplant patients receiving treatment that reduce the activity of the immune system, CMV can cause serious infection such as pneumonia, colitis, hepatitis and retinitis. Refractory or resistant CMV in patients with impaired immunity is a long-term debilitating and life-threatening condition and associated with higher death rate in transplant patients.

Maribavir, administered orally, is thought to block the action of an enzyme of the virus called UL97 kinase. By blocking the enzyme, the medicine is expected to prevent viruses from reaching maturity, so that no new infectious viruses can be produced. If licensed, maribavir would offer an alternative treatment option for patients with CMV infections that are clinically refractory and/or genetically resistant to GCV, VGCV, CDV or FOS after stem cell or solid organ transplantation.

PROPOSED INDICATION

Treatment of post-transplant cytomegalovirus (CMV) infection and disease in adults that are resistant / refractory to ganciclovir (GCV), valganciclovir (VGCV), cidofovir (CDV) or foscarnet (FOS).[1,a]

TECHNOLOGY

DESCRIPTION

Maribavir (TAK-620, SHP620) is a potent, selective, orally bioavailable benzimidazole riboside that is active against CMV infection in humans.[2] Maribavir is active in vitro against CMV strains that are resistant to current anti-CMV agents such as ganciclovir, foscarnet, or cidofovir. It has anti-CMV effects on CMV DNA synthesis, viral gene expression, encapsidation, and viral capsid egress through the inhibition of UL97-mediated phosphorylation of nuclear lamin A/C.[3] The UL97 kinase has important roles in the replication of CMV, such that genetic knockout or maribavir suppression of its function severely impairs viral growth but does not prevent it entirely.[4]

Maribavir is currently in clinical development for the treatment of CMV infection that are clinically refractory and/or genetically resistant to GCV, VGCV, CDV or FOS in stem cell transplant (SCT) and solid organ transplant (SOT) recipients. In the phase III clinical trials (NCT02931539, NCT02927067), 400 mg of maribavir (2*200 mg tablets) was administered twice daily (BID) orally for 8 weeks.[1,5,6]

INNOVATION AND/OR ADVANTAGES

Most current compounds used against CMV inhibit the CMV DNA polymerase, and resistance is caused by mutations in the CMV genes coding for UL97 protein kinase or UL54 DNA polymerase.[3] Infection with drug-resistant CMV develops in 5 to 14% of transplant recipients. The available anti-CMV agents are also limited by their toxic effects, including myelosuppression (ganciclovir and valganciclovir), nephrotoxicity (foscarnet and cidofovir), and electrolyte imbalances (foscarnet).[2] Letermovir, recently approved for CMV prophylaxis in allogeneic haematopoietic stem cell transplant (HSCT) recipients, inhibits CMV replication by binding to components of the CMV-terminase complex, but the role of letermovir in the treatment of active CMV infection (refractory/resistant or not), has not been well studied and its use would be off-licence.[3] Hence, there is a need for effective anti-CMV agents with more favourable safety profiles and different mechanisms of action.[2]

Results from a phase II clinical trial (NCT01611974) shows that maribavir ≥400 mg administered orally twice daily was effective for the treatment of refractory or resistant CMV infections among allogeneic HSCT and SOT recipients.[3,5] The treatment led to the resolution of CMV viremia in two-thirds of patients within 6 weeks of treatment. In line with previous studies, there was no evidence of dose-related myelosuppression; these data support the safety of maribavir administration for up to 24 weeks.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Maribavir does not currently have Marketing Authorisation in the EU/UK for any indication.

[a] Information provided by Takeda Ltd on UK PharmaScan

Maribavir received an orphan drug designation by the EMA in 2013 for the treatment of CMV disease in patients with impaired cell-mediated immunity.[7]

In January 2018, maribavir was granted Breakthrough Therapy Designation by US FDA for the treatment of CMV infection in transplant patients resistant or refractory to prior therapy.[8]

PATIENT GROUP

DISEASE BACKGROUND

CMV is a herpes virus and a common viral infection.[9,10] The various strains of CMV are species specific and produce a cytopathic effect resulting in greatly enlarged (cytomegalic) cells containing cytoplasmic and intranuclear inclusions.[11] Once a person is infected, CMV stays in the body for life and the person will have CMV antibodies (known as 'seropositive'). The virus is carried by around 50–80% of the population. For healthy people, CMV usually remains dormant and does not cause symptoms.[10]

CMV infections that are refractory or resistant to currently available antivirals are a major cause of morbidity and mortality among haematopoietic stem cell transplantation (HSCT) and SOT recipients.[3] Moreover, CMV-negative recipients receiving an organ from CMV-positive donors develop more frequent and more aggressive disease.[12] People with higher risk for CMV infection include pregnant women and individuals with impaired immunity, such as people on chemotherapy, transplant recipients and HIV-infected individuals.[13-15] CMV infection is a frequent complication after transplantation. The major risk factors are when the recipient is CMV seronegative and the donor is seropositive as well as when lymphocyte-depleting antibodies are used.[12]

Primary infection from CMV does not always cause symptoms in immunocompetent individuals, however, some may get flu-like symptoms the first time they catch CMV, including a high temperature, aching muscles, tiredness, feeling sick, sore throat and swollen glands.[14]. Reactivation of CMV in immunocompromised individuals is clinically severe and can cause severe and potentially lethal complications such as pneumonitis, colitis, retinitis and encephalitis.[16-18]

CLINICAL NEED AND BURDEN OF DISEASE

In 2019, 1,726 patients received allogeneic haematopoietic stem cell transplants in the UK.[19] It is reported that up to 50% of CMV seropositive recipients of allogeneic HSCT experience CMV reactivation, regardless of the donor's serostatus.[20] For HSCT, the risk of CMV reactivation is significant; highest risk of CMV is in allogeneic seropositive recipients (R+).[21] Using Polymerase chain reaction (PCR), about 60-70% of seropositive recipients reactivate CMV and develop CMV viraemia and 5-10% will develop CMV disease.[22-24] Any level of CMV is associated with increased risk of mortality in the first year post-HSCT.[22]

Over 4,700 solid organ transplants are conducted in the UK in 2019/20, most are kidney or liver.[25] CMV serostatus of donor and recipient (D/R) are key predictors of the risk of CMV infection. CMV D+/R- transplants are highest risk, and despite prophylaxis, about 20% will test positive for CMV infection, and 4-12% will develop CMV disease.[26,b] Approximately 8% of renal, 29% of liver, 25% of heart and 39% of lung transplants can be expected to experience symptomatic CMV infection. An audit from Manchester UK showed that 30% of renal recipients were high risk and that half of these experienced CMV disease.[11]

[b] Information provided by Takeda Ltd

The 2019-2020 Hospital Episodes Statistics for England recorded a total of 917 finished consultant episodes (FCE) for CMV disease (ICD-10 code: B25.9), resulting in 644 hospital admissions and 4,844 FCE bed days and 233 day cases.[27]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Cytomegalovirus (CMV) infection and CMV disease should be diagnosed according to established, internationally accepted, standardized criteria. A multidisciplinary approach to management of CMV disease is required. Risk-adapted patient assessment should inform clinical management. Once optimum human leucocyte antigen (HLA) matching has been performed, a CMV matching should be performed between patient and donor. Donors or recipients who are initially found to be CMV IgG-negative should be retested pre-transplant to exclude primary CMV infection.[9] All solid organ donors and recipients should be screened for CMV status prior to, or at the time of transplantation.[11]

Prophylactic and pre-emptive strategies have both been used to reduce the incidence of CMV disease. Universal monitoring of CMV levels in the blood is essential irrespective of whether prophylaxis is administered. Monitoring of CMV load should be undertaken at least weekly for the first 3 months post-HSCT. Drug resistance should be considered if the CMV DNA load in blood fails to respond after 14 days of therapy, especially in non-lymphopaenic or multiply pre-treated patients.[9]

The options for treating post-transplant CMV infection and disease (GCV, VGCV, CDV and FOS) are largely used off-licence. Current antiviral agents recommended for the prevention and treatment of CMV post-HSCT (though not specifically licensed for this indication) include:[9]

- Primary prophylaxis with aciclovir or valaciclovir;
- Secondary prophylaxis with valaciclovir or VGCV;
- GCV is recommended as first-line pre-emptive therapy for CMV in HSCT patients;
- FOS is recommended as an alternative first-line agent if neutropenia is present or for ganciclovir treatment failure;
- Pre-emptive therapy with CDV can be considered as third-line in patients unresponsive to, or intolerant of, both a GCV preparation and FOS;
- *De novo* CMV disease should be treated with GCV or FOS, plus intravenous immunoglobulin.

Current antiviral agents recommended for the prevention and treatment of CMV post-SOT (though not specifically licenced for this indication) are:[11]

- Prophylaxis with VGCV for certain patient populations;
- GCV or VGCV recommended first-line;
- FOS or CDV recommended as second-line options.

In SOT patients, where both donor and recipient are seronegative for CMV, no prophylaxis or monitoring is required. CMV seronegative recipients who receive a solid organ transplant from a donor who is seropositive should be offered prophylaxis against primary infection. When the donor and recipient are both seropositive and the patient is not treated with T cell depleting antibody therapy, prophylaxis is recommended for lung transplant recipients. Prophylaxis is not recommended for other types of organ transplant recipients (kidney, liver, pancreas, heart).[11]

In HSCT patients, primary prophylaxis with GCV is not generally recommended as toxicity outweighs efficacy. Intravenous immunoglobulin is not recommended for prophylaxis of CMV infection. CMV disease that develops while on pre-emptive therapy or is clinically progressive requires drug resistance testing, increased drug doses and/or combination therapy. Reduction in immunosuppression, especially reduction in corticosteroid dose, is strongly recommended when possible.[9]

CURRENT TREATMENT OPTIONS

According to NICE, letermovir is indicated for the prophylaxis of CMV reactivation or disease in people with seropositive-CMV who have had an allogeneic HSCT.[28]

GCV and VGCV have a licence for use in the treatment and/or prevention of CMV infection and disease following transplant:

- GCV is indicated in adults and adolescents from 12 years of age for the treatment of cytomegalovirus (CMV) disease in immunocompromised patients.[29]
- GCV is indicated in adults and adolescents from 12 years of age for the prevention of CMV disease in patients with drug-induced immunosuppression (for example following organ transplantation or cancer chemotherapy).[29]
- VGCV is indicated for the prevention of CMV disease in CMV-negative adults and children (aged from birth to 18 years) who have received a solid organ transplant from a CMV-positive donor.[30]

PLACE OF TECHNOLOGY

If licensed, maribavir would offer an alternative treatment option for post-transplant patients with CMV infections that are clinically refractory and/or genetically resistant to GCV, VGCV, CDV or FOS.

CLINICAL TRIAL INFORMATION

Trial	NCT02927067; 2015-004726-34; A Phase 3, Multicenter, Randomized, Double-blind, Double-dummy, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Compared to Valganciclovir for the Treatment of Cytomegalovirus (CMV) Infection in Hematopoietic Stem Cell Transplant Recipients **Phase III** - recruiting **Location(s):** EU (incl UK), USA, Canada and other countries **Primary completion date:** Jul 2021
Trial design	Randomised, parallel assignment, double-blinded
Population	N=550 (planned); subjects with CMV infection and recipients of HSCT; aged 16 years and older
Intervention(s)	400 mg of maribavir (2*200 mg tablets) twice daily (BID) orally for 8 weeks
Comparator(s)	900 mg of valganciclovir (2*450 mg tablets) BID orally 8 weeks; may be adjusted to 450 mg BID or 450 mg once a day (QD) during the study for renal function impairment or neutropaenia
Outcome(s)	Primary outcome: Proportion of participants with confirmed clearance of plasma CMV DNA (CMV Viremia Clearance) at

	the end of study week 8, regardless of whether study assigned treatment was completed [Time Frame: Week 8] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT02931539; 2015-004725-13; A Phase 3, Multicenter, Randomized, Open-label, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Treatment Compared to Investigator-assigned Treatment in Transplant Recipients With Cytomegalovirus (CMV) Infections That Are Refractory or Resistant to Treatment With Ganciclovir, Valganciclovir, Foscarnet, or Cidofovir **Phase III** – completed **Location(s):** EU (incl UK), USA, Canada, Australia, Singapore and Switzerland **Study completion date:** Aug 2020
Trial design	Randomised, parallel assignment, open-label
Population	N=352; subjects with CMV infections that are refractory or resistant to treatment with GCV, VGCV, FOS, or cidofovir; aged 12 years and older
Intervention(s)	400 mg (2x200 mg tablets) maribavir twice daily orally (doses separated by a minimum of 8 hours) for 8 weeks
Comparator(s)	Investigator-assigned treatment with GCV, VGCV, FOS, or cidofovir for 8 weeks
Outcome(s)	Primary outcome: Proportion of participants who achieve confirmed clearance of plasma CMV DNA (CMV Viremia Clearance) at week 8 [Time frame: week 8] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT01611974; A Phase 2, Randomized Study to Assess the Safety and Anti-cytomegalovirus (CMV) Activity of Different Doses of Maribavir for Treatment of CMV Infections That Are Resistant or Refractory to Treatment With Ganciclovir/Valganciclovir or Foscarnet in Transplant Recipients **Phase II** – completed **Location(s):** USA **Actual study completion date:** Dec 2014
Trial design	Randomised, parallel assignment, double-blinded
Population	N=120; stem cell or solid organ transplant recipients with cytomegalovirus infections that are resistant or refractory to treatment with GCV, VGCV, FOS, or cidofovir; aged 12 years and older

Intervention(s)	400 mg or 800 mg or 1200 mg of maribavir twice daily orally for up to 24 weeks
Comparator(s)	No comparator
Outcome(s)	Primary outcome(s): • Number of participants with confirmed undetectable plasma cytomegalovirus (CMV) within 6 weeks [Time frame: 6 weeks] • Number of participants with a treatment emergent adverse event (TEAE) [Time frame: 25 weeks] See trial record for full list of other outcomes
Results (efficacy)	See trial record
Results (safety)	See trial record

ESTIMATED COST

The cost of maribavir is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Letermovir for preventing cytomegalovirus disease after a stem cell transplant (TA591). July 2019.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages). B04/P/a.

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.[31]
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ADDITIONAL INFORMATION

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