NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Maribavir for treating refractory or resistant cytomegalovirus infection after transplant [ID3900]

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of maribavir within its marketing authorisation for treating refractory or resistant cytomegalovirus infection in people who have had a haematopoietic stem cell transplantation or solid organ transplant.

Background

Cytomegalovirus (CMV) is a common viral infection. 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% to 80% of the population.[1] For healthy people, CMV usually remains dormant and does not cause symptoms. However, for people undergoing transplants the virus can become active again (reactivation) because of a weakened immune system. Reactivation of CMV in this population can cause severe complications such as pneumonitis, colitis, retinitis and encephalitis.[2–4] CMV infections that are refractory or resistant to current treatments are a major cause of morbidity and mortality among people who have haematopoietic stem cell transplantation (HSCT) or solid organ transplant (SOT) such as heart, lung, kidney or liver transplants.[5] Additionally, people who do not carry CMV (known as 'seronegative') and receive an organ from seropositive donors are more likely to develop the disease and it can be more aggressive.[6]

In 2019, 1,714 patients received HSCT in the UK.[7] It is reported that up to 50% of CMV seropositive recipients of HSCT experience CMV reactivation, regardless of the donor's serostatus.[8] Any level of CMV is associated with increased risk of mortality in the first year after HSCT.[9] Over 4,700 SOTs were conducted in the UK between 2019 and 2020, most of which were kidney or liver transplants.[10] About 8% of renal, 29% of liver, 25% of heart and 39% of lung transplants can be expected to experience symptomatic CMV infection.

To reduce or prevent the effects of CMV infection or reactivation, people who have undergone transplants are given either universal prophylaxis or pre-emptive therapy. Prophylactic therapy is given to people who are at risk of developing CMV infection, while pre-emptive therapy is given when there is evidence of CMV replication in the blood. There are currently no treatments recommended by NICE for treating CMV infection that is refractory or resistant to other treatments. For CMV infection in people who have had a HSCT, current guidelines recommend antiviral therapy with ganciclovir, foscarnet or valganciclovir in first line setting according to individual characteristics such as ganciclovir tolerance, antiviral resistance or gastrointestinal function.[11] Foscarnet, cidofovir or ganciclovir and foscarnet combination can be used in second line, while cidofovir or ganciclovir and foscarnet combination are recommended in third line. Cytotoxic lymphocytes may be used as a last resort when all other treatments have failed. For people who have had a SOT, CMV infection is treated with ganciclovir (alone or in combination with hyperimmune globulins) or valganciclovir in first line setting, while foscarnet or cidofovir are used as second line treatment.[12] Foscarnet and cidofovir are both toxic to kidneys and may not be a

treatment option for patients with significantly impaired kidney function. So, foscarnet may be reserved for third line setting because of kidney toxicity.[12]

The technology

Maribavir (brand name unknown, Takeda) is a benzimidazole riboside that acts to block the action of the enzyme UL97 kinase in cytomegaloviruses and prevent the production of new viruses. Maribavir is administered orally.

Maribavir does not currently have a marketing authorisation in the UK for cytomegalovirus infection that is refractory or resistant to treatment. It has been studied in a clinical trial as monotherapy compared with ganciclovir, valganciclovir, foscarnet and cidofovir in people aged 12 or over with CMV infection that is refractory or resistant to treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir after HSCT or SOT.

Intervention(s)	Maribavir
Population(s)	People with cytomegalovirus infection that is refractory or resistant to treatments after haematopoietic stem cell transplantation or solid organ transplant
Comparators	• ganciclovir • valganciclovir • foscarnet • cidofovir • ganciclovir with foscarnet • ganciclovir with hyperimmune globulins • cytotoxic lymphocytes *None of the listed comparators currently have a marketing authorisation in the UK for this indication.*
Outcomes	The outcome measures to be considered include: • CMV infection symptom improvement or reduction • length of hospital stay • mortality • tissue invasive disease • transplant graft function • viral load • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	If the evidence allows the following subgroups will be considered. These include: • People who have had HSCT • People who have had SOT The availability and cost of biosimilar and generic products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** Letermovir for preventing cytomegalovirus disease after a stem cell transplant (2019) NICE Technology Appraisal 591.

Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Chapter 29. Blood and marrow transplantation services (adults and children) Chapter 56A. Hand and upper limb transplantation service (adults) Chapter 57. Heart and lung transplantation service (including mechanical circulatory support) (adults and children) Chapter 68. Islet transplantation service (adults) Chapter 69. Liver transplantation service (adults and children) Chapter 85. Pancreas transplantation service (adults) Chapter 103. Small bowel transplantation service (adults and children) Chapter 138. Stem cell transplantation service for juvenile idiopathic arthritis and related connective tissue disorders (children) 139B. Uterine transplantation services (adult women) Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1 and 3. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

References

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10 NHS Blood and Transplant. (2020) Organ Donation and Transplantation: Activity figures for the UK as at 9 April 2020. Accessed February 2021.

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