NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Maribavir for treating refractory or resistant cytomegalovirus infection after transplant

Draft scope

Draft 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 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 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. 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 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 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 alone or with hyperimmune globulins • valganciclovir • foscarnet • cidofovir • ganciclovir with foscarnet *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 clearance • CMV infection symptom improvement or reduction • mortality • recurrence rates • resistance rates • tissue invasive disease • 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 with CMV infection refractory or resistant to other treatments • People who have had HSCT or SOT • Transplant donor and recipient serostatus • Treatment resistance gene mutations 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

Questions for consultation

Is the population defined appropriately? Is the population expected to include children between 12 and 18?

Is maribavir expected to be used as pre-emptive therapy for treating CMV infection?

Have all relevant comparators for maribavir been included in the scope? Which treatments are considered to be established clinical practice in the NHS for CMV infection that is refractory or resistant to other treatments after transplant?

Are the same treatments used for refractory and resistant CMV infection? If no, which treatments are used specifically for refractory CMV infection and which treatments are used for resistant CMV infection?

Is ganciclovir used after first line to treat CMV infection that is refractory or resistant to other treatments after transplant?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'Other considerations' appropriate? Are there any other subgroups of people in whom maribavir is expected to be more clinically effective and cost effective or other groups that should be examined separately?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which maribavir will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider maribavir to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of maribavir can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

1 Medscape. Heuman DM, et al. (2019) Cytomegalovirus Colitis. Accessed February 2021.

2 Park SC, Jeen YM, Jeen YT. Approach to cytomegalovirus infections in patients with ulcerative colitis. *The Korean journal of internal medicine*. 2017;32(3):383-92.

3 Mombelli M, Manuel O. (2019) Cytomegalovirus infection. Accessed February 2021.

4 Spector SA, Davis JL. (2002) Cytomegalovirus: Second Edition. Accessed February 2021.

5 Papanicolaou GA, Silveira FP, Langston AA et al. (2019) Maribavir for Refractory or Resistant Cytomegalovirus Infections in Hematopoietic-cell or Solid-organ Transplant Recipients: A Randomized, Dose-ranging, Double-blind, Phase 2 Study. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 2019;68(8):1255-64.

6 Azevedo LS, Pierrotti LC, Abdala E et al. (2015) Cytomegalovirus infection in transplant recipients. *Clinics (Sao Paulo, Brazil)*. 2015;70(7):515-23.

7 British Society of Blood and Marrow Transplantation and Cellular Therapies. (2019) BSBMTCT Registry: 2019 Annual Activity. 2019. Accessed February 2021.

8 George B, Pati N, Gilroy N et al. (2010) Pre-transplant cytomegalovirus (CMV) serostatus remains the most important determinant of CMV reactivation after allogeneic hematopoietic stem cell transplantation in the era of surveillance and preemptive therapy. *Transplant Infectious Disease*. 2010;12(4):322-9.

9 Green ML, Leisenring W, Xie H et al. (2016) Cytomegalovirus viral load and mortality after haemopoietic stem cell transplantation in the era of pre-emptive therapy: a retrospective cohort study. *The Lancet Haematology*. 2016;3(3):e119-e27.

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

11 Ljungman P, de la Camara R, Robin C et al. (2017) 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). *Lancet Infect Dis*. 2019 Aug;19(8):e260-e272.

12 British Transplantation Society. (2015) The Prevention and Management of CMV Disease after Solid Organ Transplantation (Third Edition). Accessed February 2021.