NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Letermovir for the prophylaxis of cytomegalovirus reactivation or disease in people with seropositive-cytomegalovirus who have had an allogeneic haematopoietic stem cell transplant

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of letermovir within its marketing authorisation for preventing cytomegalovirus reactivation or disease in people with sero-positive-CMV who have had an allogeneic haematopoietic stem cell 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 50–80% of the population[1]. For healthy people, CMV usually remains dormant and does not cause symptoms. However, for people undergoing haematopoietic stem cell transplantation (HSCT) the virus can become active again (reactivation) because of a weakened immune system. CMV infection in this population can cause serious complications and increased mortality.

In 2015, 1,610 patients received allogeneic haematopoietic stem cell transplants in the UK[2]. It is reported that up to 50% of CMV seropositive recipients of allogeneic HSCT experience CMV reactivation, regardless of the donor's serostatus[3].

Prophylactic antiviral strategies aim to reduce CMV incidence. Monitoring of CMV levels in the blood is essential. Antivirals for primary or secondary prophylaxis may include aciclovir, valaciclovir, valganciclovir[4] and foscarnet. Use of ganciclovir is limited due to toxicity[4].

The technology

Letermovir (Prevymis, Merck, Sharp & Dohme) 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. It is taken orally (but may be taken intravenously in people who cannot swallow or absorb the drug from the gastrointestinal tract).

Letermovir has a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for the "prophylaxis of

cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT).". It has been studied in a phase III randomised placebo-controlled trial in sero-positive adults for the prevention of CMV infection.

Intervention(s)	Letermovir
Population(s)	Adults with sero-positive cytomegalovirus who have had an allogeneic haematopoietic stem cell transplantation
Comparators	• aciclovir (does not currently have a marketing authorisation in the UK for this indication) • valaciclovir (does not currently have a marketing authorisation in the UK for this indication) • no preventative treatment
Outcomes	The outcome measures to be considered include: • CMV infection rate • reduction of hospital in-patient days • Time to onset of clinically significant CMV infection • Time to initiation of PET for CMV viraemia • Time to all-cause mortality • overall survival • 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 subgroup will be considered: people at high risk of CMV reactivation. 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	None
Related National Policy	Management of cytomegalovirus infection in haemopoietic stem cell transplantation (2013). British Society for Haematology Guidelines NHS England, Manual for Prescribed Specialised Services 2016/1729. Blood and marrow transplantation services (adults and children) https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf NHS England Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages): Revised, NHS England, revised January 2015 https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/01/b04-haematp-stem-cll-transplt.pdf Department of Health, NHS Outcomes Framework 2015-2016, Dec 2014. Domains 1 and 3. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf

References

1. Medscape. Heuman DM, et al. Cytomegalovirus Colitis. Accessed May 2017

2. British Society of Blood and Marrow Transplantation. 2015 activity. Accessed May 2017.

3. George B, Pati N, Gilroy N et al. Pre-transplant cytomegalovirus (CMV) serostatus remains the most important determinant of CMV reactivations after allogeneic hematopoietic stem cell transplantation in the era of surveillance and preemptive therapy. Transplant Infectious Disease 2010;12:322-329. Accessed June 2017.

4. Management of cytomegalovirus infection in haemopoietic stem cell transplantation. British Journal of Haematology. Accessed June 2017