NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE
Proposed Health Technology Appraisal

Letermovir for preventing cytomegalovirus infection in sero-positive patients having allogeneic haematopoietic stem cell transplantation

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of letermovir within its marketing authorisation for preventing cytomegalovirus infection in sero-positive patients having allogeneic haematopoietic stem cell transplantation.

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 blood or bone marrow transplantation the virus can become active again (reactivation) because of a weakened immune system. This type of CMV infection 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 (brand name unknown, 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 does not currently have a marketing authorisation in the UK. It has been studied in a phase III randomised placebo-controlled trial in sero-positive adults for the prevention of clinically-significant CMV infection.

Intervention(s)	Letermovir

Population(s)	Adults with sero-positive cytomegalovirus undergoing allogeneic haematopoietic stem cell transplantation
Comparators	Antiviral treatments including: • 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) • valganciclovir (does not currently have a marketing authorisation in the UK for this indication) • ganciclovir • foscarnet (does not currently have a marketing authorisation in the UK for this indication) For people who cannot have, or are intolerant to, previous antiviral therapy • no preventative treatment
Outcomes	The outcome measures to be considered include: • CMV infection rate • reduction of hospital in-patient days • reduction in antiviral treatment duration • 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 appropriate, the appraisal should include the costs associated with diagnostic testing for CMV replication in people who are CMV seropositive and have undergone an allogeneic HSCT. A sensitivity analysis should be provided without the cost of the diagnostic test.

	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

Questions for consultation

How will letermovir be used in clinical practice?
Have all relevant comparators for letermovir been included in the scope? Is foscarnet a relevant comparator?

Which treatments are considered to be established clinical practice in the NHS for prevention of cytomegalovirus for patients undergoing allogeneic HSCT? Are treatments given in particular sequences?

Is 'no preventative treatment' a relevant comparator?

Are the outcomes listed appropriate? How is clinically-significant CMV infection and non-clinically significant CMV infection defined?

Are there any subgroups of people in whom letermovir is expected to be more clinically effective and cost effective or other groups that should be examined separately? How would you define this group of people?

Is diagnostic testing routine practice, or required, to confirm pre-emptive treatment with antivirals?

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 letermovir 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 letermovir 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 letermovir 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.

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. 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