National Institute for Health and Care Excellence

Single Technology Appraisal (STA)
Letermovir for the prophylaxis of cytomegalovirus reactivation or disease in seropositive-cytomegalovirus in people who have had an allogeneic haematopoietic stem cell transplant

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Merck, Sharp & Dohme (MSD)	MSD have concerns around the suitability of letermovir for assessment via the NICE technology appraisal process, and considers the NHSE specialised commissioning route more appropriate. The rationale being that in clinical practice letermovir would only be considered for use in a small, well defined number of patients – the specialist management of these haematological stem cell transplant (HSCT) patients in England is outlined within a current NHSE service specification and the anticipated budget impact is low and stable. The NHSE specialised commissioning process is already underway, and given the relatively small patient population and stable budget impact, MSD believe this should be the continued process for review of letermovir.	Comment noted.
Timing Issues	MSD	Letermovir is expected to be granted positive CHMP Opinion [redacted]	Comment noted.

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		There are currently no licensed treatment options for the prevention of cytomegalovirus (CMV) reactivation. From the available literature, current antivirals used for pre-emptive therapy (PET) are associated with toxicities, including myelosuppression and renal impairment. Letermovir offers a much-anticipated prophylaxis option for CMV seropositive allogeneic-HSCT patients. Letermovir has already progressed through the early stages of NHS England's application process for specialised commissioning. MSD is now concerned that the timeline required to complete a NICE technology appraisal could further delay patient access in an area of high unmet medical need.	

Comment 2: the draft scope

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Background information	MSD	The terms 'haematological stem cell transplantation' (HSCT) and 'blood or bone marrow transplantation' are used interchangeably throughout the background information. MSD would recommend consistently referencing HSCT throughout the scope, as this aligns with the draft remit, which in turn reflects the proposed indication for letermovir. The last sentence of the first paragraph in the background section states: 'This type of CMV infection can cause serious complications and increased mortality'. MSD would suggest rewording to 'CMV infection in this population can cause serious complications and increased mortality' to better reflect that the risk of these adverse outcomes is particularly pertinent to individuals that have undergone HSCT, as opposed to a specific type of CMV infection.	Comment noted. The background section is intended to present a broad overview of the disease area and the current treatment options available. An in-depth exploration of the disease area, epidemiology and current clinical practice should be reserved for when the appraisal

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		MSD would also welcome clarity on the categorisation of antivirals for prophylaxis, as per the British Society for Haematology (BSH) guidelines. These guidelines state that aciclovir or valaciclovir are choices in primary prophylaxis, and valaciclovir or valganciclovir in secondary prophylaxis. It should be emphasised that these products have no prophylaxis licence – furthermore, guidelines state that "primary prophylaxis with ganciclovir is not generally recommended as toxicity outweighs efficacy in HSCT patients	submissions are submitted.
The technology/ intervention	MSD	Letermovir is an antiviral medicinal product against CMV. Letermovir inhibits the CMV DNA terminase complex which is required for viral DNA replication. Biochemical characterisation and electron microscopy have demonstrated that letermovir affects the formation of proper unit length genomes and interferes with virion maturation. Letermovir has been studied in a phase III randomised, placebo-controlled trial in 565 patients.	Comment noted.
Population	MSD	MSD would recommend ensuring the scope defines the population as per our proposed licence, which is in [redacted]	Comment noted. The scope has been updated to reflect the relevant population.
Comparators	MSD	As prophylaxis is not currently standard practice in the management of CMV infection due to a lack of licensed options, MSD would recommend that no preventative treatment is the only appropriate comparator for letermovir. There is ambiguity around the role of the referenced antivirals. Although aciclovir is sometimes used in prophylaxis, MSD understands from clinical	Comment noted. The comparator section of the scope has been updated to reflect current clinical practice.

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		experts that it is generally included to cover other herpes simplex viruses. Aciclovir is not specifically licensed as a prophylactic agent in CMV infection and there are limited data to support its use in this indication. The BSH guidelines also state that aciclovir must be accompanied by appropriate viral load testing due to low efficacy against CMV; this indicates that it is essentially a modification of PET rather than a true prophylaxis. Ganciclovir as prophylaxis is not recommended in the BSH guidelines due to toxicity.	
Outcomes	MSD	The suggested outcome measure 'reduction in antiviral treatment duration' requires further clarity. MSD would recommend amending this to 'reduction in incidence of PET' to align with the phase III clinical trial. There are no data to support the use of letermovir in combination with other antivirals. MSD would also recommend including the following key outcome measures: • Time to onset of clinically significant CMV infection • Time to initiation of PET for CMV viraemia Time to all-cause mortality	Comment noted. The outcomes have been updated and additional outcomes added to reflect those that are clinically relevant.
Other considerations	MSD	MSD understands that in current clinical practice, the serostatus of all patients would be determined via a diagnostic test – all patients (with the exception of a donor negative, recipient negative combination) would be monitored for signs of CMV reactivation through polymerase chain reaction (PCR) testing. This testing is standard, recommended within the BSH guidelines, and not dependent on the decision to give prophylaxis versus no prophylaxis. Therefore, MSD does not consider 'no testing' a suitable scenario for a sensitivity analysis.	Comment noted. The scope has been updated and additional testing has been removed from this section.

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Innovation	MSD	Letermovir will be the only licenced antiviral option considered suitable for use as prophylaxis in this population. A shift towards prophylaxis, and away from pre-emptive therapy, would represent a clinically significant development in the management of CMV seropositive allogeneic-HSCT patients. The toxicities associated with pre-emptive therapy options are significant and well-understood; the benefits of this step-change are significant to patients and healthcare providers.	Comment noted.
Additional comments on the draft scope	MSD	**How will letermovir be used in clinical practice?** It is intended that letermovir will be initiated by consultant haematologists in CMV-seropositive adults no later than 28 days following allogeneic-HSCT, and continued for 100 days post-transplant. **Have all relevant comparators for letermovir been included in the scope? Is foscarnet a relevant comparator?** MSD considers no prophylaxis utilisation to be the most appropriate comparator, as this does not currently represent an established part of the treatment paradigm due to a lack of licensed options. There is ambiguity around the role of currently available antivirals which are used primarily as PET, as referenced above. Foscarnet is not specifically licensed for prophylaxis of CMV, but is considered for use as PET in patients with myelosuppression. However, the available literature and BSH guidelines note that it can cause renal impairment in patients. It should be excluded from scope, as any use would occur at a later stage of the patient pathway.	Comment noted. Comment noted. Comment noted.

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		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? According to both BSH guidelines and clinical expert opinion, ganciclovir is recommended as first-line PET for CMV in HSCT patients. Oral valganciclovir is considered a valid alternative when gastrointestinal absorption is normal or only minimally impaired; however, myelosuppression must be closely monitored. Foscarnet is an alternative first-line agent if neutropenia is present or for ganciclovir treatment failure. Cidofovir can be considered for PET in patients unresponsive to, or intolerant of, both a ganciclovir preparation and foscarnet.	Comment noted.
		Are the outcomes listed appropriate? How is clinically-significant CMV infection and non-clinically significant CMV infection defined? In the Phase III trial clinically-significant CMV infection was defined as either the onset of CMV end-organ disease, or initiation of anti-CMV PET based on documented CMV viraemia and the clinical condition of the patient.	Comment noted. No subgroups have been added to the scope.
		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? The Phase III clinical trial for letermovir was conducted in patients considered at high risk for CMV reinfection (CMV seropositive, adult allogeneic HSCT recipients). Letermovir demonstrated similar efficacy across all relevant patient subgroups, therefore MSD would expect letermovir to be considered in line with its full licensed indication.	Comment noted. The scope has been updated and additional

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		Is diagnostic testing routine practice, or required, to confirm pre-emptive treatment with antivirals? MSD understands that PCR testing to confirm CMV viraemia is recommended by guidelines and is routinely carried out prior to initiating PET, although the frequency of testing and protocols for initiating PET can vary between healthcare providers and treatment centres, however the overall strategy is consistent throughout the UK. Testing is conducted at least once-weekly, and more frequently in patients requiring additional monitoring. **Is 'no preventative treatment' a relevant comparator?** No prophylaxis utilisation is the most relevant comparator. There are currently no licensed treatment options for prophylaxis of CMV infection. The safety and efficacy of letermovir was evaluated in a Phase III study against a placebo arm designed to mimic PET, which is the current standard of care. Antivirals such as ganciclovir and valganciclovir are not licensed for prophylaxis and are used as pre-emptive therapy; however, they are associated with significant toxicities including myelosuppression and renal impairment. In clinical practice, they are positioned at a later stage in the patient pathway	testing has been removed. Comment noted. The comparator section of the scope has been updated to reflect current clinical practice.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
GlaxoSmithKline