

letermovir 240mg film-coated tablets (Prevymis®)

SMC No 1338/18

Merck Sharp and Dohme Ltd

8 June 2018 (*Issued 8 February 2019*)

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the ultra-orphan medicine process

letermovir (Prevymis®) is accepted for use within NHSScotland.

Indication under review: for prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT).

Letermovir, compared with placebo, reduced the incidence of CMV reactivation and disease in CMV-seropositive adults undergoing allogeneic HSCT.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of letermovir. This advice is contingent upon the continuing availability of the PAS in NHSScotland or a list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Vice Chairman
Scottish Medicines Consortium

Indication

For prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT). Consideration should be given to official guidance on the appropriate use of antiviral agents.¹

Dosing Information

Letermovir 480mg once daily. Treatment with letermovir may be started on the day of transplant and no later than 28 days post-HSCT. Prophylaxis should continue through 100 days post-transplant.

The safety and efficacy of letermovir use for more than 100 days has not been studied in clinical studies. Prolonged letermovir prophylaxis beyond 100 days post-transplant may be of benefit in some patients at high risk of late CMV reactivation. Use of letermovir prophylaxis for greater than 100 days requires a careful assessment of the benefit-risk balance.

Dosage adjustments should be consider as follows:

- If letermovir is co-administered with ciclosporin, the dosage of letermovir should be decreased to 240mg once daily.
- If ciclosporin is initiated after starting letermovir, the next dose of letermovir should be decreased to 240mg once daily.
- If ciclosporin is discontinued after starting letermovir, the next dose of letermovir should be increased to 480mg once daily.
- If ciclosporin dosing is temporarily interrupted due to high ciclosporin levels, no dose adjustment of letermovir is needed.

Letermovir should be initiated by a physician experienced in the management of patients who have had an allogeneic HSCT.¹

Product availability date

25 January 2019.

Letermovir has been designated an orphan medicine by the European Medicines Agency (EMA) for the prevention of CMV disease in patients with impaired cell-mediated immunity deemed at risk. It also meets SMC ultra-orphan criteria for this indication.

Background

Letermovir is the first in a new class of antivirals that inhibit the CMV DNA terminase complex, which is required for cleavage and packaging of viral progeny DNA. Letermovir disrupts the formation of viral genomes of an appropriate length and interferes with viral maturation.¹ It is the first medicine to be licensed for prophylaxis of CMV reactivation and disease in adult CMV-seropositive recipients of allogeneic haematopoietic stem cell transplant (HSCT).² Both oral and intravenous preparations are licensed for use, however only the oral tablet formulation is commercially available at present.

Letermovir for use in this indication has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines.

Nature of condition

CMV is ubiquitous and generally acquired early in life with the majority of the adult population being CMV-seropositive in most countries.² It is a herpes virus and primary infection is generally followed by life-long latency. Reactivation of the infection can occur when the immune system is compromised and begins with asymptomatic CMV viraemia that can progress to CMV end-organ disease, which most commonly affects the lung (e.g. pneumonitis), gastro-intestinal tract (e.g. colitis), eye, liver and central nervous system. In addition to organ specific damage CMV disease can be associated with profound, but poorly characterised, indirect immunosuppressive effects, leading to increased rates of fungal and bacterial infections and acute and chronic graft-versus-host disease (GVHD). During allogeneic HSCT, patients are immunocompromised and those with latent CMV infection are at risk of CMV reactivation, particularly during the first 100 days post-transplant.²

For CMV seropositive patients undergoing HSCT the guideline from the British Committee for Standards in Haematology (BCSH), British Society of Blood and Marrow Transplantation (BSBMT) and UK Virology Network recommends that secondary prophylaxis should be considered in conjunction with prolonged CMV viral screening. Treatment options for secondary prophylaxis include valganciclovir (2g three times daily) or valganciclovir (900mg daily). The other approach noted in the guideline also involves regular monitoring of CMV in the blood with initiation of pre-emptive therapy (PET) when low level CMV viraemia is detected. Ganciclovir is recommended as first-line PET for CMV in HSCT patients. Oral valganciclovir is a useful alternative when gastrointestinal absorption is normal or only minimally impaired. Foscarnet is as an alternative first-line agent if neutropenia is present or for ganciclovir treatment failures.³ Clinical experts have advised that in Scotland patients undergoing allogeneic HSCT would receive off-label prophylaxis using oral aciclovir 800mg four times daily during conditioning chemotherapy and then switched to aciclovir 10mg/kg intravenously three times daily on the day prior to receiving stem cells. Once engrafted, patients are converted back to oral aciclovir prior to discharge.

Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely for effective treatment options, as the efficacy of high-dose aciclovir is limited. It was highlighted that CMV reactivation (despite aciclovir) in high-risk patients post-allograft is a major contributor to transplant-related morbidity and mortality. It was noted that CMV levels are monitored twice weekly. If these start to rise, and the patient has robust blood counts, they may receive oral valganciclovir as an out-patient. However, often the immune system is too immature or levels are above the treatment threshold and the patient would receive intravenous ganciclovir, foscarnet or cidofovir as an in-patient, typically for at least two weeks.

A patient and clinician engagement (PACE) meeting was held to consider the added value of letermovir in the context of treatments currently available in NHS Scotland. At the meeting attention was drawn to the fact that reactivation of CMV post-transplant is a serious life-threatening condition that can be associated with substantial morbidity and can affect multiple organs, e.g. pneumonitis, retinitis, colitis, encephalitis. Treatment for reactivation of CMV can be burdensome for patients, since it usually requires treatment in hospital for at least two weeks, and can be associated with additional procedures to monitor and treat any end-organ disease. Only

valgancicovir can be given orally but can this reduce white cell counts leading to issues with infection. The other treatments (ganciclovir, foscarnet and cidofovir) are given intravenously and can be associated with unpleasant and potentially serious side-effects, particularly nausea/vomiting, electrolyte disturbances and renal, liver and blood toxicity, which may require monitoring and management. It was noted that there are no licensed or other effective therapies for prevention of reactivation of CMV post-transplant.

Impact of new technology

Summary of evidence on comparative efficacy

A double-blind phase III study (PN001) recruited 570 CMV IgG-positive adults who had a first allogeneic HSCT within the preceding 28 days and had undetectable CMV DNA (confirmed by central laboratory). They were stratified by study centre and risk of CMV reactivation, then randomised in a 2:1 ratio to receive letermovir 480mg (240mg if taking ciclosporin), orally or intravenously (at discretion of site investigators), once daily or placebo. Treatment was initiated within 28 days of HSCT and continued until week 14 post-transplant (approximately 100 days). The primary outcome was the proportion of patients through to week 24 who developed clinically significant CMV infection, defined as onset of CMV end-organ disease or initiation of pre-emptive therapy (PET) based on CMV viraemia (by central laboratory) and patient's clinical condition. The protocol suggested thresholds for initiation of PET were 150 copies/mL for high risk patients in the first 14 weeks and 300 copies/mL for low risk patients in the first 14 weeks and for both high and low risk patients after week 14. The primary outcome was assessed in the full analysis set, which comprised all randomised patients who received at least one dose of study drug and had no detectable CMV DNA at initiation of study treatment. In the primary analysis patients who discontinued early or had missing data at week 24 were considered to have had a primary outcome event, i.e. prophylaxis failure.^{2,4}

In the letermovir group compared with placebo group significantly fewer patients had clinically significant CMV infection or were considered as having a primary end point by week 24: 38% (122/325) versus 61% (103/170), respectively, with a difference of -24% (95% confidence interval [CI]: -32% to -15%), $p < 0.0001$. Events contributing to this and the key secondary outcome are detailed in table 1. The between group difference in the primary outcome was mainly due to a difference in initiation of PET for CMV viraemia, as there were low rates of CMV end-organ disease and rates of discontinuation and missing data were similar across the groups. The key secondary outcome, proportion of patients with clinically significant CMV infection through week 14 (same definition as primary outcome), was significantly lower with letermovir compared with placebo: 19% (62/325) versus 50% (85/170), difference -31% (95% CI: -40% to -23%), $p < 0.001$. There appears to be a catch-up of CMV viraemia and CMV disease within the letermovir group after discontinuation of letermovir at week 14. The rate of clinically significant CMV infection between weeks 14 and 24 was higher in the letermovir group compared with placebo and this was due mainly to CMV viraemia and CMV disease.^{2,4}

Table 1: Primary and key secondary outcome of PN001 study: clinically significant CMV infection through week 24 and 14.^{2,4}

	Week 24		Week 14	
	Letermovir (N=325)	Placebo (N=170)	Letermovir (N=325)	Placebo (N=170)
Primary outcome, n (%)	122 (38)	103 (61)	62 (19)	85 (50)
• Clinically significant CMV infection	57 (18)	71 (42)	25 (7.7)	67 (39)
(a) Initiation of PET	52 (16)	68 (40)	24 (7.4)	65 (38)
(b) CMV end-organ disease	5 (1.5)	3 (1.8)	1 (0.3)	2 (1.2)
• Discontinued study before week 24	56 (17)	27 (16)	33 (10)	16 (9.4)
(a) Due to adverse event	6 (1.8)	1 (0.6)	5 (1.5)	1 (0.6)
(b) Due to death without CMV	28 (8.6)	12 (7.1)	14 (4.3)	6 (3.5)
(c) Due to other reasons	22 (6.8)	14 (8.2)	14 (4.3)	9 (5.3)
• Missing data at week 24 visit	9 (2.8)	5 (2.9)	4 (1.2)	2 (1.2)

CMV = cytomegalovirus; PET = pre-emptive therapy.

Hospital admission rates were exploratory endpoints. Hospitalisation for CMV-related disease in the letermovir and placebo groups through week 24 was 3.1% (10/325) versus 7.6% (13/170), respectively, with the majority in the first 14 weeks within the placebo group, 7.1% (12/170), but not in the letermovir group, where 0.6% (2/325) occurred in the first 14 weeks post-HSCT.²

All-cause mortality was an exploratory endpoint, with no pre-specified statistical analysis. Death rate at week 24 was 12% (40/325) in the letermovir group and 19% (32/170) in the placebo group, p-value = 0.0401 (not corrected for multiplicity); at week 48, it was 23% (76/325) in the letermovir group and 27% (46/170) in the placebo group, p-value = 0.2117 (not corrected for multiplicity). The EMA review highlighted a post-hoc analysis of all-cause mortality at week 48 within the group of patients who had a primary outcome at week 24, indicating a lower rate in the letermovir group versus placebo 21% versus 34%. In the group of patients who did not have a primary outcome at week 24, the mortality rate at 48 weeks in the letermovir and placebo groups was 24% and 22%.²

Summary of evidence on comparative safety

In the treatment phase (to last dose of study medication) in PN001 study within the respective letermovir and placebo groups there were similar rates of adverse events, 98% (365/373) and 100% (192/192); which were treatment-related in 17% (63/373) and 12% (23/192), and serious adverse events, 44% (165/373) and 47% (90/192), which were treatment-related in 0.8% (3/373) and 1.6% (3/192). Fewer patients in the letermovir group compared with placebo group discontinued study medication due to an adverse event, 19% (72/373) versus 51% (98/192). Across the letermovir and placebo groups there were similar rates of treatment-related discontinuations of study medication due to adverse events, 4.8% (18/373) and 3.6% (7/192).²

During the treatment phase the most commonly reported adverse events in the letermovir and placebo groups were; GVHD (39% and 39%), diarrhoea (26% and 24%), nausea (26% and 23%) vomiting (19% and 14%), rash (20% and 21%) and pyrexia (21% and 22%). The following adverse events were reported more frequently with letermovir compared with placebo, cardiac disorders (13% versus 6.3%), ear and labyrinth disorders (4.6% versus 1.0%), myalgia (5.1% versus 1.6%), hyperkalaemia (7.2% versus 2.1%) and dyspnoea (8.0% versus 3.1%) and the following were reported less frequently with letermovir, CMV infection (8.3% versus 46%), upper abdominal pain (4.0% versus 8.3%), gastro-oesophageal reflux disease (1.1% versus 4.7%), myopathy (0.5% versus 2.6%), dehydration (0.5% versus 2.6%) and presyncope (0.3% versus 2.1%), respectively.² The most frequently reported serious AEs in the letermovir and placebo groups

were; GVHD (9.9% and 10%), recurrent acute myeloid leukaemia (2.9% and 3.6%), CMV infection (2.7% and 6.8%), acute kidney injury (1.3% and 4.7%), pneumonia (2.1% and 1.6%) and pyrexia (1.9% and 2.1%).²

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

In the pivotal study, PN001, the primary outcome, clinically significant CMV infection, measured both CMV disease and low-level CMV viraemia that prompted initiation of PET. As the majority of events met the latter criterion, the primary outcome mainly assessed avoidance of PET. Rates of the primary outcomes were significantly lower with letermovir, compared with placebo, at the primary analysis at 24 weeks (38% versus 61%) and the key secondary analysis at 14 weeks (19% and 50%). There was some catch-up in the letermovir group after treatment was stopped at week 14, as rates were higher in this group between weeks 14 and 24. The EMA review noted that clinical relevance of CMV reactivation depends upon the patient's immune status and in general clinical consequences decrease with increasing length of time since HSCT.²

Initiation of PET may require admission to hospital. The exploratory outcome, hospitalisation for CMV-related disease, had lower rates for letermovir compared with placebo at week 14 (0.6% versus 7.1%) and week 24 (3.1% versus 7.6%), with the majority of events in the placebo group occurring before week 14 and most in the letermovir group after week 14. All-cause mortality, also an exploratory outcome was limited by lack of pre-specified statistical analysis. It was not significantly different between the groups at week 48. However, the EMA review highlighted a post-hoc analysis of all-cause mortality at week 48 within the group of patients who had a primary outcome at week 24, indicating a lower rate in the letermovir group versus placebo (21% versus 34%). In the group of patients who did not have a primary outcome at week 24, the mortality rate at 48 weeks in the letermovir and placebo groups was 24% and 22%, respectively. It was hypothesised that delaying onset of CMV reactivation to a phase when patients are less fragile may be associated with mortality similar to those without CMV reactivation. However, as there is no evidence that the differences in mortality were due to CMV disease, this suggestion remains speculative.²

The comparator in study PN001 was placebo, however, according to SMC clinical experts the medicine most likely to be displaced in NHS Scotland is off-label high dose aciclovir. The company conducted a systematic literature review of antiviral agents for the indication under review but considered that an indirect comparison was not feasible. Within study PN001 patients were permitted to receive antivirals for prophylaxis of herpes simplex virus and varicella zoster virus: aciclovir (at doses up to and including 3200mg daily), valaciclovir (at doses up to and including 3000mg daily) and famciclovir (at doses up to and including 1500mg daily).² The generalisability of the study may be limited, since the placebo group of PN001 is not reflective of current Scottish practice.

Subgroup analyses were consistent with the primary outcome across subgroups defined by risk category for CMV reactivation (i.e. high versus low risk, stem cell source, donor mismatch and haploidentical donor) patient characteristics (i.e. age, gender, weight, region and time from randomisation to transplant), conditioning regimen and immunosuppressive regimen.²

Letermovir is an inhibitor of viral terminase complex. Unlike currently marketed anti-CMV medicines, which act via inhibition of the viral DNA polymerase, terminase inhibitors interfere with viral DNA maturation and packaging of monomeric genome units. Consequently, cross-resistance

is not expected between letermovir and other medicines used for treatment of CMV infection. Also, there is no known mammalian counterpart of the viral terminase complex.²

The introduction of letermovir could allow recipients of allogeneic HSCT to avoid the initiation of PET with ganciclovir, which may be clinically relevant. The EMA review noted that the safety profile of letermovir as prophylaxis is more beneficial than ganciclovir as PET.² Also, a reduction in PET could reduce the need for re-hospitalisation.

Clinical experts consulted by SMC considered that letermovir for the prophylaxis of CMV reactivation and CMV disease is a therapeutic advancement as it is an effective option in the prophylaxis of CMV reactivation in allogeneic HSCT recipients. They consider that it would be used in practice in accordance with the licensed indication.

At the PACE meeting, it was noted that by preventing reactivation of CMV, letermovir, would save patients from the risk of the potentially life-threatening complication, substantial morbidity of CMV infection and the psychological impact of facing a prolonged unpleasant treatment on patients who have already had extensive treatment for their initial serious diagnosis followed by transplant, which is a complex and risky procedure lasting about 4 to 6 six weeks (or longer if the patient has complications). Letermovir may prevent patients from having to undergo treatment for CMV reactivation, which usually involves prolonged hospitalisation and has the potential for serious side-effects. Patients may require procedures and associated hospital admissions to monitor and treat complications of CMV infection such as endoscopies or biopsies. CMV reactivation can lead to a reduced quality of life associated with CMV infection and its treatment. It can result in a delay in returning to active life, carer responsibilities, work and social life and impact on the ability of the patients and/or their carer to maintain work or carer responsibilities and may lead to subsequent financial difficulties. Since there is only one transplant centre in Scotland, prolonged treatment at this centre will have a greater impact on patients geographically remote from it. Patients have noted that they particularly value their time at home with family.

It was also noted that there is no alternative medicine of proven benefit in reducing the risk of reactivation of CMV. An unlicensed treatment (aciclovir) is used currently, but CMV reactivation rates remain significant. Letermovir (480mg [i.e. two 240mg tablets] once daily) has a lower tablet burden than aciclovir (800mg [i.e. one 800mg tablet or two 400mg tablets] four times a day). A benefit of letermovir prophylaxis is that it has a substantially better tolerability profile and is more manageable compared with the prolonged unpleasant medicines used to treat reactivated CMV infection (i.e. it is a much kinder regimen).

*Other data were also assessed but remain commercially confidential.**

Patient and clinician engagement (PACE)

A PACE meeting with patient group representatives and clinical specialists was held to consider the added value of letermovir as an ultra-orphan medicine in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Stem cell transplant is an intensive and risky intervention. Anything that makes it safer and less demanding for the patient requires consideration.
- Letermovir is the only effective treatment available to prevent CMV reactivation, which is a potentially life-threatening condition with substantial morbidity.
- Treatment for CMV reactivation is burdensome for patients, since it typically requires prolonged hospitalisation. Current treatments carry a risk of serious side-effects that may require to be monitored and managed.
- Letermovir prophylaxis regimen is a less toxic and more convenient regimen compared with medicines used to treat reactivated CMV infection.
- Prevention of CMV reactivation and associated treatment of this infection and its complications would have benefits for the patient and carer's quality of life. The patient would be well and able to live an active life assuming their usual work or carer responsibilities. Correspondingly the carer would benefit from this and the absence of additional responsibilities associated with the patient having a prolonged hospital treatment, which have a greater impact if the patient's home is geographically remote from the one transplant centre in Scotland.
- Prevention of CMV reactivation would have a positive psychological impact on the patient and carer resulting from the patient being well, able to contribute to family, work and social life. They would also avoid the stress of facing a prolonged unpleasant treatment associated with CMV reactivation, which is particularly difficult in the context of having already undergone extensive treatment for their initial serious diagnosis and endured the complex and risky treatment of stem cell transplant.

Additional Patient and Carer Involvement

We received patient group submissions from Anthony Nolan. Anthony Nolan is a registered charity. Anthony Nolan has received 0.05% pharmaceutical company funding in the past two years with none from the submitting company. Representatives from Anthony Nolan participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Value for money

The submitting company presented a cost-utility analysis comparing letermovir with standard care. This was defined as a PET strategy, with patients initiated on antivirals based on CMV viraemia levels, or to treat CMV disease. The company also noted there are currently no other licensed treatment options for CMV prophylaxis available in Scotland. The health economic case failed to factor in the use in Scotland, as noted above, of off-label high dose aciclovir (oral/IV) as prophylactic therapy. This treatment is the therapy most likely to be displaced.

A decision analytic model was used to compare the cost-effectiveness of letermovir with standard care, over a lifetime time horizon. Clinical outcomes from the pivotal study (PN001) at weeks 14 and 24 were used to model CMV status, PET therapy initiation and mortality, with data at week 48 used to model CMV re-hospitalisations, adverse events and GVHD. Each outcome was associated with direct costs and quality of life. Results were reported as incremental total costs and quality adjusted life-years (QALYs).

In the model, the life expectancy of survivors was extrapolated to lifetime. Mortality after week 24 was estimated by applying a weighted average of the annual relative risk of mortality for patients with the underlying indications post-transplant, to the life expectancies of the general population. The only disease state modelled beyond the first year was GVHD, with all survivors assumed to have a 30% risk of chronic GVHD.

A weighted average baseline utility for all patients in the pivotal study was adopted in the model. Changes from baseline as reported at weeks 14, 24 and 48 of the study were also modelled. Thereafter, patients were assumed to have a utility value which was the lower of:

- 0.82 as identified from a study of 92 patients with acute myeloid leukaemia who underwent an HSCT in a hospital in Rotterdam.
- Age-specific general population utilities from a published study.

The analysis included all medicine costs, including those for PET therapy, to manage GVHD and opportunistic infections. All administration and hospitalisation costs were also included. Costs of treating adverse events associated with PET therapy were included but not those associated with letermovir.

A patient access scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS a simple discount is offered on the list price.

The base case results with the PAS discount applied are presented in Table 2.

Table 2: Base case results with PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
SoC	£29,273	7.01	6.00	-	-	-
Letermovir	£34,470	7.46	6.41	£5,198	0.41	£12,665

ICER, incremental cost-effectiveness ratio; LYG, Life-year gained; QALY, quality-adjusted life year; SoC, standard care.

Results for key sensitivity analyses are presented in Table 3. The ICERs were sensitive to mortality rates, duration of letermovir therapy, duration of PET therapy, age and time horizon.

Table 3: Key sensitivity analyses

Model input	ICER with PAS
Base case	£12,665
Standard care all-cause mortality probability (24 week) 95% confidence intervals 10.2%, 21.6% (base case 15.9%)	£211,192 to £7,791
Mean age (years) varied between 18 and 78 years (base case 51 years)	£5,801 to £88,936
Letermovir all-cause mortality probability (24 week) 95% confidence intervals 6.8%, 13.6% (base case value 10.2%)	£9,044 to £25,817
Average days of letermovir therapy 100 per SmPC (base 72 days)	£20,131
5 year time horizon	£23,370
Medicine dose and duration consistent with those administered in PN001	£18,956
Average days of PET 59 days based on PN001; (base case 21 days)	-£3,472
Lifetime based on week 48 data	£13,591
All cause mortality only at week 48	£15,682
Non-completer = failure approach to managing missing data	£15,418

The main weaknesses are:

- The comparator in the health economic model (no prophylaxis but use of PET) is not representative of current Scottish clinical practice, in which high dose aciclovir is used. While recognising that there are limitations to the efficacy of high dose aciclovir, to the extent that this therapy is effective, the health economic case may overestimate the incremental benefit of letermovir. However, following discussions at SMC and based on feedback from SMC clinical experts, the Committee considered it may be reasonable to assume the efficacy of off-label aciclovir in this patient group is limited and therefore standard of care could be considered a reasonable proxy comparator.
- The base case results did not model actual medicine use from the pivotal study but rather data on the length of treatment on letermovir for the UK cohort (n = 12, randomized 2:1 to letermovir or placebo) of PN001 (72 days). Using the mean medicine usage in the study increased the ICERs to £18,956 with the PAS discount.

More minor weaknesses, the effects of which were tested through sensitivity analysis, include:

- Use of 24-week data in the model when week 48 data were sometimes available. The ICER with PAS increased to £15,682 when all-cause mortality at week 48 was assumed in the model.
- The two statistical methods applied to adjust for missing data in the pivotal study were weak. Adopting multiple imputation methods showed the efficacy results were likely to be in between the results from these approaches. The ICERs with the PAS discount for the two methods ranged from £12,665 to £15,418.
- Inconsistency between days of PET therapy assumed in model (21 days) which was based on expert opinion, compared with the 59 days observed in the pivotal study. With the longer

duration of PET therapy, letermovir, with the PAS discount, dominated standard care being cheaper and yielding more QALYs.

- Mean life expectancy of under 10 years in each arm was low compared with data published from a large dataset of similar patients. Increasing life expectancy would favour letermovir and reduce the ICER.
- No loss of utility from chronic GVHD was modelled after year 1, but the ICER was not sensitive to this.
- The model is a simple decision tree which only captures any impact of CMV status after year 1 on mortality and chronic GVHD. However, it is unclear whether the approach used has introduced any bias.

Impact beyond direct health benefits and on specialist services

At the PACE meeting it was noted that by preventing reactivation of CMV, letermovir, would save carers from:

- the psychological impact and stress of the patient remaining unwell.
- the additional burden of taking the patient to hospital appointments or visiting the patient if they have a prolonged admission to hospital. As there is only one transplant centre in Scotland, in Glasgow, prolonged treatment there will have a greater impact on patients remote from it.
- the strain of managing financial or carer responsibilities that the patient usually undertakes.
- pressure to cope with their own work or carer responsibilities while dealing with the additional responsibilities resulting from the patient remaining unwell.

Letermovir was not expected to be associated with additional monitoring or significant additional resources for service provision. It could potentially lead to less use of hospital resources to treat CMV infection and end-organ disease.

Costs to NHS and Personal Social Services

The company estimated there would be 42 patients eligible for treatment with letermovir in year 1, rising to 49 patients in year 5. This assumed there are currently 65 to 75 allogeneic HSCT procedures undertaken each year in Scotland, with this number rising at 3.8% per year. Of these, 54% are assumed to be CMV-seropositive.

With PAS

The company estimated the gross impact on the medicines budget to be £37k in year 1, rising to £240k in year 5. The net medicines budget was estimated at £19k in year 1, rising to £124k in year 5.

The submitting company did not estimate any costs outside the NHS.

Conclusion

The Committee also considered the benefits of letermovir in the context of the SMC decision modifiers that can be applied and agreed that the criterion for the absence of other treatments of proven benefit was satisfied. In addition, as letermovir is an ultra-orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted letermovir for use in NHS Scotland.

Additional information: guidelines and protocols

In May 2013 the British Committee for Standards in Haematology (BCSH), British Society of Blood and Marrow Transplantation (BSBMT) and UK Virology Network, published a guideline for management of CMV infection in HSCT. The guideline notes that primary CMV infection (i.e. in CMV IgG-negative patients) is followed by life-long latency, when CMV reactivation can occur, for example, when patients have a compromised immune system. Initially the reactivated infection may present asymptotically as an increase in viral CMV and can progress to CMV disease, which is characterised by end-organ damage commonly affecting the gastrointestinal tract, lungs, eye, liver or central nervous system. The guidelines recommend primary prophylaxis with aciclovir or valganciclovir, but only with appropriate monitoring of CMV in the blood. For patients who have had previous CMV disease prior to transplant or with recurrent episodes of CMV infection, especially in the context of T-cell depletion or GVHD, then secondary prophylaxis should be considered in conjunction with prolonged CMV viral screening. Valganciclovir (2g three times daily) or valganciclovir (900mg daily) were considered to be valid treatment options for secondary prophylaxis with appropriate monitoring of CMV in the blood. The current mainstay for managing CMV infection after HSCT consists of PET, which involves the rapid introduction of therapy based on evidence of CMV replication in the blood. The success of PET is dependent on the availability of rapid sensitive assays that allow early treatment at low levels of viral infection. Ganciclovir is recommended as first line PET for CMV in HSCT patients. Oral valganciclovir is a useful alternative when gastrointestinal absorption is normal or only minimally impaired. Foscarnet is recommended as an alternative first-line agent if neutropenia is present or for ganciclovir treatment failures. Lastly, cidofovir can be considered as third-line in patients unresponsive or intolerant of ganciclovir or foscarnet.³

Additional information: comparators

Clinical experts advise that allogeneic HSCT are carried out at one centre in Scotland, where recipients are given off-label aciclovir 800mg orally four times daily or 10mg/kg intravenously three times daily as prophylaxis of CMV reactivation.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per 100-day course (£)
Letermovir	240mg* to 480mg orally once daily	13,297 to 26,594
Aciclovir	10mg/kg intravenously three times daily**	9,000
Aciclovir	800mg orally four times daily**	122

*Doses are for general comparison and do not imply therapeutic equivalence. Costs from the company submission for letermovir and eVadis 3rd February 2018 for aciclovir. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration. Doses based on a body weight of 70kg. *240mg is used when ciclosporin is administered concomitantly. ** off-label use as advised by SMC clinical experts.*

References

1. Merck, Sharp, Dohme Ltd. Summary of product characteristics for letermovir (Prevymis®), last updated 8 January 2018
2. European Medicines Agency. European public assessment report for letermovir (Prevymis®), Committee for Medicinal Products for Human Use (CHMP) Assessment report, EMA/CHMP/490007/2017, 9 November 2017
3. Emery V, Zuckerman T, Jackson G et al. Management of cytomegalovirus infection in hematopoietic stem cell transplantation. *Br J Haematol* 2013; 162: 25-39
4. Marty FM, Ljungman P, Chemaly R et al. Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation. *N Engl J Med* 2017; 377(25): 2433-44
5. Commercial in Confidence*

This assessment is based on data submitted by the applicant company up to and including 29 January 2019.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:

http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in

determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.