NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Letermovir for preventing cytomegalovirus disease after a stem cell transplant

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using letermovir in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Note that this document is not NICE’s final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE’s guidance on using letemovir in the NHS in England.

For further details, see NICE’s guide to the processes of technology appraisal.

**The key dates for this appraisal are:**

Closing date for comments: 25 July 2018

Second appraisal committee meeting: 8 August 2018

Details of membership of the appraisal committee are given in section 5.
1 Recommendations

1.1 Letermovir is not recommended, within its marketing authorisation, for preventing cytomegalovirus (CMV) reactivation and disease after an allogeneic haematopoietic stem cell transplant (HSCT) in adults who are seropositive for CMV.

1.2 This recommendation is not intended to affect treatment with letermovir that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Current management of CMV after an allogeneic HSCT (a stem cell transplant from a donor) involves regular blood tests to monitor CMV levels (with or without aciclovir). If CMV levels rise, treatment with ganciclovir, valganciclovir or foscarnet (pre-emptive therapy) is started to prevent disease but this can cause severe side effects. Letermovir is an option for reducing CMV and has a better safety profile than pre-emptive therapy.

Clinical trial evidence shows that letermovir is effective in reducing CMV infection. It also reduces the need for pre-emptive therapy. But it is uncertain whether letermovir reduces mortality from CMV disease. Also, there are concerns about how relevant the trial data are to NHS clinical practice.

The most plausible cost-effectiveness estimates are above £20,000 per quality-adjusted life year (QALY) gained and higher than £30,000 per QALY gained in some scenarios. But the estimates are affected by small changes in letermovir’s mortality benefit, the magnitude of which is
uncertain. Because of this letermovir cannot be recommended for preventing CMV reactivation or disease in adults who have had an allogeneic HSCT and are seropositive for CMV.

2  Information about letermovir

<table>
<thead>
<tr>
<th>Marketing authorisation</th>
<th>Letermovir (Prevymis, Merck, Sharpe &amp; Dohme) is indicated ‘for the prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive [R+] recipients of an allogeneic haematopoietic stem cell transplant’.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration and dosage</td>
<td>The recommended dose of letermovir is 480 mg once daily (oral tablets or intravenously), decreasing to 240 mg once daily if co-administered with cyclosporin A. Treatment with letermovir may be started on the day of transplant or on any day up to 28 days afterwards and should continue for 100 days after transplant; longer treatment may be considered in some patients at high risk for late CMV reactivation.</td>
</tr>
<tr>
<td>in the marketing authorisation</td>
<td></td>
</tr>
<tr>
<td>Price</td>
<td>The price was submitted as commercial in confidence because the product has not yet been launched. The company has a commercial arrangement which would apply if the technology had been recommended.</td>
</tr>
</tbody>
</table>

3  Committee discussion

The appraisal committee (section 5) considered evidence submitted by Merck, Sharpe & Dohme and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Clinical need

Cytomegalovirus reactivation can have a substantial effect on mental health and wellbeing for patients and their families

3.1  Cytomegalovirus (CMV) can become active again in about 60 to 80% of people who are seropositive for CMV and who have had an allogeneic HSCT, especially if it involved T-cell depletion therapy, which is common in the UK. The patient experts highlighted that this reactivation of CMV
can have a substantial psychological effect on patients and their families. Hospital admissions to treat CMV infection disrupt family and working life and are particularly stressful because of the worry and risk of further infections. For most people CMV reactivation has a negative effect on their mental health and wellbeing. Treatment for CMV infection with pre-emptive therapy (see section 3.2) can have serious side effects. The patient experts highlighted that better prevention of CMV reactivation would reduce hospital admissions and exposure to toxic pre-emptive therapy. The committee concluded that CMV reactivation can have a substantial psychological effect on patients and their families.

**Clinical management**

**A new treatment that could prevent CMV reactivation and reduce the need for pre-emptive therapy would be welcomed by patients and clinicians**

3.2 There are no licensed treatments available specifically for preventing CMV reactivation after an allogeneic HSCT. The current standard approach in the NHS is surveillance monitoring for viral reactivation. When viral DNA is detected, pre-emptive therapy is started using ganciclovir, valganciclovir or foscarnet, depending on the type of transplant received (T-cell depletion or T-cell repletion). The clinical experts stated that practice varies for when to start pre-emptive therapy. Some centres would base this on a specific viral load count but the clinical experts explained that assays for measuring viral load are not standardised. Aciclovir is also used as prophylaxis in some centres although the clinical experts explained that it is not effective for this. The clinical experts stated that letermovir reduces reactivation rates and the need for toxic pre-emptive therapy and improves quality of life. The committee concluded that an effective treatment that specifically acts to prevent CMV reactivation would benefit people who are seropositive for CMV who have had an allogeneic HSCT.
Clinical evidence

The main evidence is from PN001, a randomised, double-blind, placebo-controlled trial

3.3 The main clinical evidence came from a phase 3 randomised placebo-controlled trial, PN001. This trial compared the efficacy and safety of letermovir (n=373) with placebo (n=192) in adults who were seropositive for CMV and who have had an allogeneic HSCT. Treatment continued to week 14 (~100 days) and patients were monitored through to week 24 post-transplant for the primary efficacy endpoint. The primary outcome was the incidence of clinically significant CMV infection by week 24, as assessed by the proportion of people with CMV end-organ disease or starting anti-CMV pre-emptive therapy (ganciclovir, valganciclovir or foscarin with or without cidofovir) based on documented CMV viraemia (as measured by the central laboratory) and the clinical condition of the patient. Patients who completed the trial subsequently entered a follow-up phase from week 24 to week 48 after transplant. The company presented results for 2 populations: the overall randomised population who had treatment, also known as the ‘all subjects as treated’ population and the ‘full analysis set’ population, which was the main analysis population in the trial. The full analysis set population excluded patients who were randomised and had treatment if they had detectable CMV DNA on day 1.

To account for missing data, the company’s preferred approach was to assume that if people did not complete treatment their treatment had not worked. This included people with missing data or who stopped the study early. The committee concluded that PN001 was a well conducted trial but it had some concerns about the generalisability of the trial to UK practice (see section 3.4).
The generalisability of the PN001 trial results to clinical practice in England is uncertain

3.4 Although the committee agreed that PN001 was a well conducted trial, it was concerned about how generalisable its results were to NHS practice. It considered the following limitations:

- Only 12 patients were from the UK.
- The maximum treatment duration was 100 days. The ERG considered this inappropriate because in clinical practice, some people may need longer periods of prophylaxis, for example people having treatment for active graft versus host disease or those at high risk of CMV reactivation because of T-cell depletion. The clinical experts explained that although the marketing authorisation allows treatment after 100 days, they do not recommend it because there is no evidence supporting such use.
- There was a delay (mean 11.5 days, all subjects as treated population; mean 10.9 days, full analysis set population) in starting prophylaxis after transplant in the trial, which could potentially underestimate the efficacy and treatment duration of letermovir. The clinical experts stated that they would not expect a delay in starting letermovir prophylaxis immediately after HSCT in clinical practice.
- The prevalence of ciclosporin A use in people who received letermovir in the trial was 51.7% (based on the all subjects as treated population). Both the ERG and the clinical experts at the committee meeting agreed that this was much lower than seen in clinical practice. They assumed that approximately 90 to 95% of people would have ciclosporin A and the remaining patients would have tacrolimus.
- The limited use of alemtuzumab (used for depleting T-cells to avoid graft versus host disease) in the trial (4%) compared with clinical practice in the NHS (around 60 to 85%) could potentially underestimate the CMV reactivation rate and overestimate the risk of graft versus host disease. The clinical experts stated that its use in clinical practice
depends on the treating centre but suggested that approximately 60 to 85% of people would have alemtuzumab.

- The ERG highlighted that clinically significant CMV infection leading to pre-emptive therapy is defined differently in the trial than in UK practice. In the trial, a viral load threshold between 150 to 300 copies/ml was used, depending on the patient’s risk of CMV infection. The clinical experts stated that, in clinical practice, the threshold varied by centre but typically would be between 400 to 700 copies/ml. The committee noted that the trial could therefore be overestimating the CMV infection rate and the use of pre-emptive therapy.

The committee considered that the issues around generalisability of the PN001 trial results to clinical practice in England made interpreting the results challenging but the committee acknowledged that these factors could individually overestimate and underestimate the efficacy of letermovir. It concluded that these issues should be taken into account in its decision-making.

**Letermovir reduces CMV infection at 24 weeks after allogeneic HSCT**

3.5 In PN001, letermovir statistically significantly reduced the rate of clinically significant CMV infection at week 24 compared with placebo. The stratum-adjusted treatment difference between letermovir and placebo was −23.5 (95% confidence interval [CI] −32.5 to −14.6). The hazard ratio (HR) for time to onset of clinically significant CMV infection at week 24 was 0.29 (95% CI 0.21 to 0.42). There was also a statistically significant difference in starting pre-emptive therapy for documented viraemia by week 24 between letermovir and placebo (stratum-adjusted treatment difference −23.3 (95% CI −32.3 to −14.3)). The committee concluded that compared with placebo, letermovir is effective in reducing the incidence of clinically significant CMV infection after allogeneic HSCT and in reducing the need for pre-emptive therapy.
The all-cause mortality benefit of letermovir compared with placebo is not statistically significant at 48 weeks

3.6 In PN001, letermovir statistically significantly reduced the all-cause mortality rate at week 24 compared with placebo, with a HR of 0.57 (95% CI 0.34 to 0.96). The company also did an exploratory analysis using week 48 data, which included people who withdrew early from the trial but were confirmed to be alive after the trial had ended. The difference in all-cause mortality between letermovir and placebo was 3.8% but this was not statistically significant (HR 0.73, 95% CI 0.49 to 1.09). When people were stratified by prior CMV infection in another ad hoc analysis, people on letermovir who had clinically significant CMV infection through week 24 had a lower all-cause mortality rate at week 48 when compared with people on placebo who had clinically significant CMV infection at week 24. Similar all-cause mortality rates were seen in both treatment groups in people without clinically significant CMV infection at week 24. The committee acknowledged that these ad hoc analyses could suggest that letermovir prevents additional CMV-related all-cause mortality, despite not completely preventing CMV reactivation. It also noted that CMV-related mortality results were available but that the European Medicines Agency did not consider the data to be scientifically sound. Clinical experts stated that a mortality benefit with letermovir is plausible although it has not been proven. The committee concluded that the 48-week post hoc analysis provided a more complete data set for decision-making but the size of letermovir’s all-cause mortality benefit is uncertain because of the many uncertainties and differences highlighted between the trial and clinical practice (see section 3.4), and the limited follow-up of mortality benefit. Also, any mortality benefit associated with avoiding CMV reactivation was not known.
Adverse events

The safety profile of letermovir is acceptable

3.7 Overall, adverse events were similar between the letermovir group and the placebo group except for those leading to patients stopping treatment. There were no treatment-related deaths in either group. The most commonly reported adverse events in the 2 groups were graft versus host disease, nausea, vomiting, diarrhoea, pyrexia and rash. Cardiac disorder, hyperkalaemia, ear and labyrinth disorder and dyspnoea were more common in people on letermovir than on placebo. The ERG commented that the adverse event results were difficult to interpret because of the underlying conditions and treatments as well as the toxicity associated with various pre-emptive therapy regimens. Also, there were no safety data for letermovir use after 100 days. The committee was aware of the conclusions in the European public assessment report, which stated that the adverse event profile appeared similar to that of current standard care (that is, surveillance monitoring and pre-emptive therapy). The committee concluded that the safety profile of letermovir was acceptable and unlikely to be worse than current standard care.

Health-related quality of life

PN001 did not show a health-related quality-of-life benefit for letermovir compared with placebo

3.8 Results measured at the time of randomisation and at weeks 14, 24 and 48 after transplant using EQ-5D-3L and FACT-BMT questionnaires showed that there were no statistically significant differences in health-related quality of life between letermovir and placebo. A small possible utility benefit on graft versus host disease, rehospitalisation and opportunistic infections was seen with letermovir compared with placebo but these were not formally tested. The ERG also highlighted that other than at randomisation, the mean values for EQ-5D-3L and FACT-BMT
scores represent a mixture of those who have had CMV reactivation and started pre-emptive therapy and those who have not. The direct effect of letermovir on health-related quality of life was therefore confounded. Also, the clinical experts stated that showing improvement in quality of life in a clinical trial of this nature is challenging because of differences in timing of assessments in relation to letermovir dosing and administration of other treatments. The health-related quality-of-life results from PN001 are therefore difficult to interpret. The committee acknowledged the limitations in the trial, which made interpreting the results more challenging. The committee agreed that there could plausibly be a health-related quality-of-life benefit associated with preventing CMV reactivation but concluded that the trial did not show this.

**Cost-effectiveness model structure**

The company’s modelling approach is over simplified but appropriate for decision-making

3.9 The company’s economic model had a lifetime time horizon and consisted of a decision tree phase up to week 24 after transplant (week 48 in the scenario analysis) and a simple 2-state (alive or dead) Markov model phase covering the remaining time horizon of the model. The ERG considered that the modelling approach taken by the company was too simplistic because it lacked explicit health states to capture differences in quality-adjusted life years (QALYs). This approach does not link the rate of CMV events (the principal benefit of letermovir) with mortality. The committee was aware that this meant that nearly all the QALY benefits in the model for letermovir were derived from mortality differences. As such, the difference in the rate of CMV infection and other clinical events (for example, graft versus host disease) between the letermovir group and the placebo group and their effect on quality of life and mortality could not be fully explored. The committee agreed with the ERG that the company’s modelling approach was over simplified. It also acknowledged that this
introduces uncertainty about the true clinical and cost-effectiveness estimates. Nevertheless, the committee recognised the difficulty in fully capturing the mortality benefits associated specifically with letermovir prophylaxis in the model because of the differences in mortality risk associated with patients’ underlying conditions and the lack of available data to do this. The committee concluded that although the model is oversimplified, it was appropriate for decision-making.

**Clinical data in the economic model**

The clinical data used for the decision tree phase of the company's economic model is not based on the most complete data set

3.10 In the decision tree phase of the model, the company included the cumulative probabilities of 6 different clinical events from PN001 (starting pre-emptive therapy, CMV disease, rehospitalisation, opportunistic infection, graft versus host disease and all-cause mortality). These clinical events were drawn from the 24-week data and used ‘data as observed’, meaning that no adjustments were made for the 13.5% incomplete follow-ups at week 24. The ERG considered it inappropriate to use 24-week data when 48-week data were available for most outcomes. The committee recalled that the company had collected mortality data at week 48, which included people who withdrew early from the trial but were confirmed to be alive after the end of the trial. The ERG considered this data set to be more complete because only 3.2% patients were lost to follow-up. The committee agreed with the ERG and preferred the 48-week data to be used instead of the 24-week ‘data as observed’ used in the company’s model.

**Mortality data from the haematological malignancy research network (HMRN) is more relevant to clinical practice**

3.11 In the company’s model in the Markov model phase, the clinical outcome used was all-cause mortality. The mortality rate was assumed to be the
same in both groups. This was based on general population mortality data from the Office for National Statistics, with a standardised mortality rate from Wingard et al. (2011) applied to account for the effect of the underlying condition. The ERG considered that the company’s general approach was appropriate but that the HMRN was a more relevant source of UK data. The clinical experts at the committee meeting agreed. In the company’s model the excess risk of mortality in year 2 was assumed to be equal to the excess risk in year 3. The clinical experts stated that mortality risk in year 2 was likely to be much higher than in year 3 and more in line with that reported by the HMRN (19% compared with the company’s 3%). Also, the ERG highlighted that the data in the Wingard study were relatively old (from 1980 to 2003) and therefore its relevance to current practice was unclear. In addition, a substantial proportion (more than 40%) of the trial population in the Wingard study were from paediatric populations. The committee therefore concluded that the HMRN data are more relevant to NHS clinical practice.

**Utilities in the economic model**

**The ERG’s approach to modelling long-term disutility associated with HSCT is preferred for decision-making**

3.12 The company submitted a scenario analysis that included a disutility for the long-term effects (more than 48 weeks) of HSCT. However, the ERG did not consider this analysis to fully capture the long-term disutility associated with having HSCT because it was derived from a mix of EQ-5D-5L (Leunis et al. 2014) and EQ-5D-3L (Ara et al. 2011) values. The ERG suggested an alternative disutility based on the difference between the mean utility of patients in PN001 at 48 weeks and the mean general population utilities obtained from Ara et al. The committee agreed that the company’s approach to modelling long-term disutility associated with HSCT was inappropriate and concluded that the ERG’s alternative approach was preferable.
Disutility associated with graft versus host disease should be included in the company's base case

3.13 The ERG identified that the disutility associated with graft versus host disease should have been included in the company’s base-case analysis because it was a serious and common complication of allogeneic HSCT and was associated with significant morbidity and mortality. The committee agreed that the disutility associated with graft versus host disease should have been included in the model.

Resource use and costs

The company's assumption about treatment duration is likely to be underestimated

3.14 The company assumed that the mean duration of treatment in the model was 69.4 days. This was based on the all subjects as treated population. The ERG considered that the duration of treatment may be considerably longer. In the ERG’s base case the mean duration of treatment was assumed to be 83 days. This was based on the duration of therapy in the full analysis set population (72.1 days) plus an additional 10.9 days from the delayed start of prophylaxis in the trial. The clinical experts explained that because a delay in starting letemovir prophylaxis is not expected in clinical practice, the duration of treatment is likely to be longer than 69.4 days but should not be more than 100 days (see section 3.4). The clinical experts supported the ERG’s use of 83 days as the mean duration of treatment. The committee therefore agreed that the ERG’s assumption for the treatment duration was more plausible than the company’s.

The ERG’s assumption about intravenous letemovir use is overestimated

3.15 Based on the administration route used in the 12 UK patients in PN001, the company model assumed that approximately 5% of patients would have intravenous letemovir. However, the ERG considered that the proportion of patients in PN001 who had intravenous letemovir (27%)
was more representative of UK practice. The clinical experts explained that because T-cell depletion is commonly used in current practice, they tend to use treatments that are less toxic to the gut. Therefore, they agreed with the company’s assumption that only 5% of patients would have intravenous letemovir. The committee agreed that the company’s assumption about intravenous letemovir use was more appropriate than the ERG’s.

**Foscarnet use should be between 15 and 25%**

3.16 The ERG was concerned that the assumed use of foscarnet (25%) in the company’s model was too high, potentially overestimating the cost of pre-emptive therapy. It heard from its clinical experts that only 5 to 15% of patients would have foscarnet as part of their pre-emptive therapy. However, the clinical experts at the meeting stated that its use varied between centres and often depends on the type of transplant received. For example, people having T-cell depletion, which is common in NHS practice, would most likely have foscarnet because of their higher risk of earlier CMV reactivation. Therefore, the clinical experts suggested that the use of foscarnet is closer to 15 to 25%. The committee concluded that foscarnet use in the model should be between 15 and 25%.

**Cost-effectiveness estimates**

**The company’s base-case ICER comparing letemovir with standard care is £10,904 per QALY gained**

3.17 The company’s deterministic base-case incremental cost-effectiveness ratio (ICER) was £10,904 per QALY gained for letemovir compared with placebo. The committee agreed that the company’s base case was not appropriate for decision-making because of concerns about the following inputs and assumptions in the model:

- The use of 24-week data over 48-week data because this may overestimate the mortality benefit of letemovir (see section 3.10).
The use of both full analysis set and all subjects as treated data.

- The use of mortality rates based on the Wingard et al. study (see section 3.11).
- Treatment duration is likely to be underestimated in the model (see section 3.14).

The ERG’s preferred assumptions increase the ICER

3.18 The ERG incorporated a number of changes to the company’s model to produce its own base-case ICER. These included:

- Using the full analysis set population for all clinical parameters.
- Using 48-week trial data together with the post hoc analysis of all-cause mortality (see sections 3.6 and 3.10).
- Assuming mean duration of therapy to be 83 days (see section 3.14).
- Including medium-term care management costs for survivors of HSCT and alternative survivor disutility.
- Including costs and disutilities associated with graft versus host disease (see section 3.13).
- Including relapsed disease based on the HMRN rate of relapse (47% compared with 10% in company’s scenario analysis).
- Including a one-off administration cost for oral letermovir and valganciclovir, using revised intravenous administration costs for foscarnet and ganciclovir and assuming intravenous letermovir use to be 27% instead of 5%.
- Assuming foscarnet use to be 15% instead of 25% (see section 3.16).
- Basing the mortality data in the Markov phase of the model on HMRN data and relative risk from Martin et al. (2010), which included fewer paediatric patients and had a longer median follow-up than Wingard et al. (see section 3.11).

The committee noted that combining the ERG’s preferred assumptions substantially increased the ICERs compared with the company’s base
case. The ERG’s preferred deterministic base-case ICER for letermovir compared with placebo was £27,536 per QALY gained.

A scenario analysis on the ERG’s preferred base case highlights the sensitivity of the ICER to mortality

3.19 The ERG did an additional scenario analysis on its preferred base case, considering the uncertainty around the following assumptions and inputs used in the model:

- duration of therapy
- the approach used to model missing data
- mortality at 48 weeks.

The committee noted that even a small change to a key assumption could have a large effect on the ICER. In particular, to the mortality rate, where increasing it by 1% (that is, from 3.8% to 4.8%) decreases the ICER from £27,536 to £23,124 per QALY gained, but decreasing the mortality rate by 1% (from 3.8% to 2.8%) pushes the ICER from £27,536 to £34,471 per QALY gained if all of the ERG’s preferred assumptions are incorporated.

The most plausible ICER is above £20,000 per QALY gained and possibly above £30,000 per QALY gained

3.20 Having considered the ICERs using the ERG’s preferred assumptions, the committee took into account its preferred assumptions that differed from the ERG’s base case:

- Foscarnet to be used for 15 to 25% of patients, in line with the clinical experts’ opinion (see section 3.16). The committee acknowledged that this would decrease the ICER from the ERG’s preferred analysis.
- Intravenous letermovir to be used for 5% of patients, in line with the clinical experts’ opinion (see section 3.15). The committee acknowledged that this would decrease the ICER from the ERG’s preferred analysis.
• The committee considered that concomitant use of ciclosporin A would be closer to 90%, in line with the clinical experts’ opinion (both the company and the ERG assumed 95%). It acknowledged that this would increase the ICER from the ERG’s preferred analysis.

• The committee considered that the company’s preferred approach in the efficacy analyses to account for missing data was the most plausible approach (both the company and the ERG’s base cases used the ‘data as observed’ approach). It acknowledged that this would increase the ICER from the ERG’s preferred analysis from £27,536 to £30,179 per QALY gained.

The committee recalled that it considered the generalisability of the trial data to clinical practice to be uncertain (see section 3.4) and the economic model to be too simplistic (see section 3.9). It also recalled that the ICER was very sensitive to the estimate of all-cause mortality and a small change could result in substantial changes to the ICER (see section 3.19). Also, there were no data specifically on CMV-related mortality. The committee concluded that the ICER was very uncertain. The true ICER was likely to be between £23,124 and more than £30,000 per QALY gained when incorporating its preferred assumptions.

**Letermovir is not recommended as a cost-effective use of NHS resources**

3.21 Having agreed that the most plausible ICER was above £20,000 per QALY gained, the committee referred to NICE’s [methods guide](#). It recalled that above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources would take into account the degree of certainty around the ICER. In particular, the committee would be more cautious about recommending a technology if it was less certain about the ICERs presented. The committee recalled its consideration that the trial may not have fully captured the health-related quality of life benefits with letermovir (see section 3.8). It also recalled that the company’s model was too
simplistic in that it lacked explicit health states to capture differences in QALYs (see section 3.9). However, the committee considered that accounting for this would not lower the ICERs to an acceptable level, especially considering the substantial uncertainty surrounding the estimates of mortality benefit, which contribute to most of the QALY gain in the model. Because of this, the committee concluded that letermovir is not recommended as a cost-effective use of NHS resources.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Professor Gary McVeigh
Chair, Appraisal Committee
June 2018

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.
The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

**NICE project team**

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

_Aimely Lee_
Technical Lead

_Christian Griffiths_
Technical Adviser

_Kate Moore_
Project Manager

ISBN: [to be added at publication]