NICE National Institute for Health and Care Excellence

NICE guidance

Maribavir for treating refractory cytomegalovirus infection after transplant

Technology appraisal guidance
Published: 18 January 2023

www.nice.org.uk/guidance/ta860

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Maribavir is recommended, within its marketing authorisation, as an option for treating cytomegalovirus (CMV) infection that is refractory to treatment including cidofovir, foscarnet, ganciclovir or valganciclovir in adults who have had a haematopoietic stem cell transplant or solid organ transplant. It is recommended only if the company provides it according to the commercial arrangement.

Why the committee made these recommendations

After a transplant, for CMV infection that does not respond well enough to treatment, usual treatment is cidofovir, foscarnet, ganciclovir or valganciclovir, or combinations of these.

Clinical evidence suggests that maribavir gets rid of CMV infection better than usual treatment, but this is uncertain because of the way the trial was done.

The most likely cost-effectiveness estimates are also uncertain. But they are towards the lower end of the range that NICE considers an acceptable use of NHS resources, and current treatment options are limited. So maribavir is recommended.

2 Information about maribavir

Marketing authorisation indication

2.1 Maribavir (Livtencity) is indicated for 'the treatment of cytomegalovirus (CMV) infection and/or disease that are refractory (with or without resistance) to one or more prior therapies, including ganciclovir, valganciclovir, cidofovir or foscarnet in adult patients who have undergone a haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT)'.

2.2 The dosage schedule is available in the summary of product characteristics for maribavir.

Price

2.3 The list price of 56 x 200 mg maribavir tablets is £11,550 (excluding VAT; company source). The company has a commercial arrangement. This makes maribavir available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Takeda, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

Clinical need

There are limited treatment options for CMV and an oral treatment given at home would be beneficial

3.1 Cytomegalovirus (CMV) is present in approximately 60% to 70% of the population. Although it is generally mild and treatable, CMV can become active when a person's immunity is weakened, such as by immunosuppressive chemotherapy or after a transplant. Latent CMV can also be transferred from a transplant donor to the recipient. Currently, there are few treatments for CMV after a transplant, and treatment resistance can be an issue. Several antiviral therapies, including valganciclovir, ganciclovir, foscarnet and cidofovir, are used off-label. But there are no licensed medicines in the UK for treating CMV infection after a solid organ transplant (SOT) or allogeneic haematopoietic stem cell transplant (HSCT) if the infection is refractory to treatment. The patient experts explained that CMV reactivation can substantially negatively affect mental health and physical wellbeing in people and their families. Hospital admissions to treat CMV reactivation can be stressful, especially after the heavy burden of transplant procedures. Refractory or resistant CMV infections can have serious effects on quality of life. Intravenous treatments are needed several times a day, which can result in extended hospitalisation. Other comorbidities and further infections can develop during treatment for CMV. All of this can delay recovery. The clinical experts explained that foscarnet can be associated with kidney damage, making it less suitable for people who have had a kidney transplant or who have impaired renal function. Cidofovir can cause neutropenia. These risks mean that, in some people whose infection is resistant or refractory to ganciclovir and valganciclovir, these medicines

have to be reused because of a lack of alternative treatment options. The patient experts suggested that the psychological benefits of being able to have treatment at home would greatly improve the recovery process from both CMV infection and transplant, avoid the unpleasant side effects of current treatment options, and also reduce costs to the NHS. The clinical experts considered that maribavir would be especially suitable for people with refractory CMV whose comorbidities mean that side effects from current second-line antiviral options would be particularly unfavourable. The committee concluded that current treatment options are limited, and an oral treatment given at home would be beneficial.

Clinical evidence

The conduct and design of SOLSTICE could bias the results

3.2 The main clinical evidence came from SOLSTICE. This was a phase 3, randomised, open-label, active-controlled trial with a 20-week follow up. Its aim was to evaluate the efficacy and safety of maribavir (n=235) compared with any of the investigator-assigned antiviral treatments (IAT, n=117). These included intravenous ganciclovir, foscarnet, cidofovir and oral valganciclovir. The choice of IAT was at the investigators' discretion and could include monotherapy or combination therapy with any of the 4 treatments. The ERG noted some concerns around the design and conduct of the trial. The open-label design meant that participants and investigators were aware of the choice of treatment from the start of the study. In the comparator arm, the investigators could choose treatment based on medical history and the clinical course of previous treatment for CMV. The investigators decided whether participants should continue previous therapy at the same or an increased dose, change treatment or select combination therapy. The investigators could also decide whether immunosuppressant therapy should be changed. The ERG considered this could lead to bias, especially for assessing recurrence. At the investigators' discretion, people having IAT could stop treatment after the third week (because of lack of efficacy or toxicity) and receive maribavir treatment instead, known as the rescue arm. The ERG thought that the rescue arm may introduce bias to some outcomes. The

committee considered that 3 weeks of treatment may not be long enough to assess whether efficacy is maintained. The clinical experts explained that in clinical practice, people are likely to stay on treatment for longer before stopping. The committee concluded that some aspects of the conduct and design of SOLSTICE could bias the results.

Results of SOLSTICE may not be generalisable to clinical practice

3.3 The committee considered how generalisable SOLSTICE was to clinical practice. It discussed the following concerns:

- One of the clinical experts advised that as time since transplant increases, the risk of CMV reactivation and other events decreases as people recover and the need for immunosuppressant therapy reduces. The mean and median time since transplant at randomisation were longer than would be expected in clinical practice for the SOT subgroup, and imbalanced between the treatment arms for SOT and HSCT. The impact of this was greater in the HSCT population because the time between transplant and randomisation was shorter than in the SOT group. There was no clear reason why the baseline characteristics should be imbalanced, given the data presented. The committee considered whether this was because of individual participant characteristics, or because of the way the trial was done. It agreed further details of the data distribution would be helpful. The length of time since transplant at randomisation in the SOT subgroup and the imbalance between treatment arms in the HSCT population would likely have a large impact on the generalisability of the SOLSTICE results to clinical practice.

- The ERG noted that many people having IAT had retreatment with an anti-CMV treatment to which their infection was resistant. It considered this would underestimate clearance in people having IAT compared with clinical practice and overestimate the relative effect of maribavir. Clinical advice to the ERG had suggested that resistance would be assessed if an infection did not respond adequately to a specific anti-CMV treatment, and that an alternative treatment would be offered. Continued treatment when resistance has been confirmed is likely to lead to a lower chance of CMV clearance than changing to an alternative treatment. At technical engagement, the company did a sensitivity analysis that excluded people who received IAT to which their infection was resistant at baseline. These results suggested that the benefit of maribavir was sustained. The company suggested that many people may have treatment to which their infection is resistant, because resistance testing is not routine practice, and because alternative treatment options may not be available because of the renal toxicity associated with some treatments (see section 3.1). It considered this would explain why investigators continued treatment even if the virus had a mutation that was known to confer resistance. The clinical experts confirmed that this was plausible.

- The ERG considered there was a large amount of missing data for clearance and clinically relevant recurrence during the trial period. At technical engagement, the company accepted there was potential for bias because of premature treatment discontinuations. It did several sensitivity analyses to control for the missing data, which showed a statistically significant benefit of maribavir compared with IAT. The company did not provide additional analyses for recurrence data because it believed there was very little missing recurrence data. Missing data could affect both clearance and recurrence outcomes. The committee considered that more data was missing in the IAT arm because of treatment discontinuation and the option for people to join the rescue arm. This missing data potentially reduced the usefulness of the time-to-event data on clearance and recurrence that would otherwise have been helpful to inform the committee's view on the effectiveness of maribavir.

  The committee concluded that the results from SOLSTICE may not be generalisable to clinical practice.

SOLSTICE data suggests that maribavir improves clearance compared with IAT, but the results are highly uncertain

3.4 The primary outcome in SOLSTICE was viral clearance at week 8. In the intention to treat population, 55.7% of people who had maribavir had confirmed CMV viraemia clearance at the end of week 8 compared with 23.9% who had IAT. After adjusting for transplant type (SOT versus HSCT) and baseline plasma CMV DNA viral load (low versus intermediate or high), the difference was 32.8% (95% confidence interval [CI] 22.8% to 42.7%; p<0.001). At the end of the trial, in people whose infection responded by week 8, fewer people on maribavir had a clinically relevant recurrence than those who had IAT, although the difference was not statistically significant. There was no statistically significant difference in all-cause mortality between treatment arms. More deaths occurred in the HSCT group than in the SOT group, and there was a small difference in favour of maribavir for SOT, but in favour of IAT for HSCT. The committee concluded that SOLSTICE suggests an advantage for maribavir achieving clearance. But because of uncertainties in the SOLSTICE data (see sections 3.1 and 3.2), it could not be sure that the data was robust enough to confirm the size of this benefit.

The company's economic model

The health states used in the company's model are appropriate

3.5 The company used a 2-stage Markov model to estimate the cost effectiveness of maribavir compared with IAT. Each health state was associated with different costs, quality of life and mortality risks. The stage 1 model included 3 health states: clinically significant CMV, no clinically significant CMV, and death. All people entered the model with clinically significant CMV. When the CMV infection cleared they could move to the no clinically significant CMV state or experience a CMV recurrence. Tunnel states were used to estimate time-dependent transitions between clinically significant and no clinically significant CMV. The stage 2 model comprised 2 health states: alive and dead. People could die at any point during either stage. The model had a lifetime time horizon, with stage 1 lasting 78 weeks. At the first meeting, the

committee agreed that the overall model structure and health states used by the company in both stages of the model were appropriate, but that it had some concerns about the duration of stage 1 of the model (see section 3.9). In response to consultation, the company updated its stage 1 Markov model by restricting it from 78 weeks to 39.2 weeks (see section 3.9). The committee concluded that the company's modelling of maribavir was appropriate.

The company's updated model using OTUS data is suitable for decision making

3.6 The company used data from OTUS to update its stage 1 model at technical engagement. OTUS is a retrospective real-world evidence analysis of CMV infection that is refractory or resistant to treatment, with a longer follow up than SOLSTICE. The company used the OTUS data to populate the model beyond the 20-week duration of SOLSTICE. This included modelling recurrences for the first 20 weeks based on SOLSTICE data, then using OTUS data to model outcomes for the remaining stage 1 time horizon. The ERG considered OTUS to be more generalisable to clinical practice than SOLSTICE, but had concerns with the way the company used the OTUS data, which assumed that the populations and outcomes in OTUS and SOLSTICE were interchangeable. The ERG highlighted that the ratio of SOT to HSCT procedures, percentage of clearance, and time since transplant differed between the 2 sources. The ERG preferred to use OTUS to model the probability of clearance and recurrence for IAT in the stage 1 Markov model, with the outcomes for maribavir estimated by applying a relative treatment effect taken from SOLSTICE. OTUS could also be used to inform risk of mortality, time since transplant and event rates of complications such as graft failure and graft-versus-host disease. In a scenario analysis done by the company using the OTUS data, clearance rates were adjusted for 8-week mortality. The ERG was unclear about why this had been done, and preferred to use data that had not been adjusted for mortality at 8 weeks. The committee preferred the ERG's approach. At the first meeting, it agreed that using OTUS data as far as possible, with the relative treatment effect of maribavir from SOLSTICE, would be more robust for modelling outcomes in the stage 1 Markov model, and that data from OTUS should not be adjusted for mortality at 8 weeks. In

response to consultation, the company incorporated OTUS data in its revised analyses, with the relative treatment effect of maribavir from SOLSTICE. The company noted the uncertainties of incorporating 2 data sources in the model, but maintained that SOLSTICE was the most reliable data source to estimate the treatment effect of maribavir compared with standard care. The ERG commented that the company had not provided the underlying data for clearance events for the SOT population, and queried the company's estimate of probability of clearance for the HSCT population. Ahead of the second committee meeting, the company submitted additional data from OTUS. The ERG was satisfied with the company's update and noted that it had a minimal effect on the incremental cost-effectiveness ratio (ICER). The committee concluded that the data used in the company's model was suitable for decision making.

Using a treatment-independent risk of recurrence is suitable for decision making

3.7 The company modelled different risks of CMV recurrence dependent on the treatment received. People having maribavir had a lower probability of CMV recurrence than those receiving IAT, even if they had experienced clearance for the same amount of time. The ERG stated that the risk of CMV recurrence should depend on the time spent in clearance rather than the treatment received, and included this in its updated model. One of the clinical experts advised that clearance with maribavir may be greater than with IAT, meaning reinfection is less likely to occur. The committee considered this reasonable, but had not seen any supporting evidence. It agreed at the first meeting that the risk of recurrence should not be treatment specific. In response to consultation, the company noted that there was evidence of an effect of maribavir on the risk of CMV recurrence. But despite this, it updated its base case and applied treatment-independent recurrence risk. The ERG agreed that the company's approach was in line with the committee's preferences. The committee concluded that using a treatment-independent risk of recurrence is suitable for decision making.

Restricting the model to 2 CMV recurrences is appropriate

3.8 The company's model included multiple CMV recurrences based on OTUS data, which showed up to 6 recurrences after SOT and 4 recurrences after HSCT. The company assumed that the risk of third and further recurrences in the model was the same as that for second recurrences. The ERG noted that in OTUS, the risk of subsequent recurrences decreased with the number of recurrences and that the benefit of maribavir may be overestimated. The ERG limited its model to 2 recurrences because no robust data was identified to inform the risk of recurrence beyond this point. The committee accepted that the risk of CMV recurrence is likely to decrease with the number of recurrences, but that more than 2 recurrences are plausible. At the first meeting it agreed that the company's model likely overestimated the number of CMV recurrences, and that it would have preferred to have seen recurrence risk decrease as the number of recurrences increased. In response to consultation, the company updated its base case, restricting the stage 1 Markov model to 39.2 weeks (see section 3.9) and 2 CMV recurrences. The company noted that the OTUS data provided evidence for multiple recurrences and that the ERG's approach of limiting the number of recurrences in the model was conservative. The company highlighted that, because it had updated its base case in this way, it was now fully aligned with the committee's preferences. The ERG agreed. The committee concluded that restricting the model to 2 recurrences was likely to be conservative, but in the absence of further data, this was the most suitable approach for decision making.

Restricting the stage 1 Markov model to 39.2 weeks is appropriate for decision making

3.9 The company originally used 20-week data from SOLSTICE to model CMV recurrences up to 52 weeks, meaning its stage 1 Markov model had a duration of 52 weeks. But based on the OTUS data (which provided evidence for multiple recurrences over a longer time), the company increased the duration of the stage 1 model to 78 weeks. The ERG was unclear about the company's reasoning for using 78 weeks. The company explained that OTUS data in the SOT population provided evidence that would allow the stage 1 model to be extended beyond

78 weeks, but had applied 78 weeks as a pragmatic option because of heterogeneity in the treatment pathway at longer time horizons and to mitigate uncertainty. The ERG highlighted there were few third (or further) recurrences in OTUS and so to model further recurrences the company had to use the risk of second recurrence from OTUS (see section 3.8). This created uncertainty in the modelling. The ERG thought that the duration of the stage 1 Markov model should reflect the time frame over which the first and second recurrences happened in OTUS (39.2 weeks) because the data for this was robust. It included this assumption in its base case. The committee recognised there was some uncertainty around the appropriate duration of the stage 1 Markov model. But it considered that if OTUS was used as the main source of data for the IAT arm of the model, the stage 1 Markov model should accurately reflect the time to last recurrence in OTUS. The committee agreed at the first meeting that the stage 1 Markov model should align with the duration of time that CMV recurrences can be accurately modelled. It specified that more than 2 CMV recurrences should be modelled, with the risk of recurrence decreasing as the number of recurrences increases, if data was available to model this. In the absence of robust data, the stage 1 Markov model should be restricted to 39.2 weeks and 2 CMV recurrences, and scenario analyses should be done to show the potential impact of further CMV recurrences, with a stage 1 duration of between 39.2 and 78 weeks. In response to consultation, the company accepted the committee's preference, and updated its base case to restrict the stage 1 Markov model to 39.2 weeks and 2 CMV recurrences. The company commented that the OTUS data was a robust source for modelling recurrences over time and that including a maximum of 2 recurrences was conservative. The committee noted that the company had not provided any scenario analyses showing the potential impact of more than 2 CMV recurrences with a stage 1 duration of between 39.2 and 78 weeks, as requested at the first meeting. The ERG was satisfied that the company had updated the model correctly. The committee concluded that the company's updated model was suitable for decision making.

Maribavir may have an impact on mortality, but this is highly uncertain and the magnitude of the impact is unknown

3.10 The company had originally modelled survival in the stage 1 Markov model using individual patient data from SOLSTICE to estimate the risk of mortality in the clinically significant CMV and no clinically significant CMV health states. But the ERG noted that the Kaplan–Meier data, which incorporated the difference in CMV events across treatment arms, showed no statistically significant difference in overall mortality between maribavir and IAT (see section 3.4). So this was inconsistent with the company's approach of assuming there was a difference in mortality for clinically significant CMV compared with no clinically significant CMV. At technical engagement, the company reiterated its view that the SOLSTICE data was the most appropriate source. It provided Kaplan–Meier data for time to all-cause mortality from SOLSTICE (adjusted to account for people in the IAT arm crossing over to have rescue treatment). The company did not explain how the adjustment was done, so the ERG could not validate the adjusted survival data. The company considered that its analysis supported using the unadjusted SOLSTICE data in the model. It reiterated its view that SOLSTICE suggested that mortality for maribavir was lower than for IAT, and that this justified using CMV-related mortality risks taken from SOLSTICE in the model. Additionally, the company provided 2 scenario analyses based on OTUS and using published data to inform mortality risks for people who had clinically significant CMV and no clinically significant CMV. The ERG noted that the scenario using the published data (Hakimi et al. [2017] for the SOT population and Camargo et al. [2018] for the HSCT population) did not include populations that fully aligned with either SOLSTICE or the decision problem. At the first meeting, the committee recognised there was a lot of uncertainty in the assumptions for mortality in the stage 1 model, but that SOLSTICE had not shown a survival benefit. It considered that mortality should not differ based on treatment, so there should be no life year gain with maribavir in the model. It agreed that risk of mortality in the stage 1 model should be the same for the maribavir and IAT groups. In response to consultation, the company disagreed with the committee's preference, and maintained that SOLSTICE provided clear evidence of a difference in survival associated with a response to CMV treatment. It provided further

evidence including a Kaplan–Meier plot of overall survival by clearance status at week 8 from SOLSTICE, which showed a statistically significant difference in the hazard rate of death between CMV clearance at week 8 (in either treatment group) compared with no CMV clearance. It also provided data from TAK620-5004, a retrospective study collecting follow-up data at 12 months from SOT and HSCT recipients randomised to the maribavir arm in the SOLSTICE study. This data showed numerically lower overall mortality than that seen in published estimates, 12 months after treatment for refractory or resistant CMV after a transplant. The company updated its base case using the published data from Hakimi and Camargo to inform mortality risks for people with clinically significant CMV and no clinically significant CMV. The ERG noted that the risk of mortality associated with CMV was likely higher in the 2 sources used in the company's base case than in SOLSTICE and OTUS, and that the company's base case represented the best-case scenario. The ERG would have preferred this data to come from OTUS had it been available. It agreed with the company that clinically significant CMV is associated with increased mortality, but not with the magnitude modelled by the company. To help with decision making, the ERG provided 2 scenarios: a worst-case scenario with no additional risk of mortality from CMV (aligned with the committee's preference after the first meeting) and a midpoint in which people with CMV were arbitrarily assumed to have twice the risk of mortality than people without CMV. The committee acknowledged that although eliminating clinically significant CMV may reduce mortality, this did not mean that maribavir would reduce mortality. It was also aware that assuming a mortality benefit associated with no CMV substantially affected the cost-effectiveness results. The committee accepted that it was very likely that CMV clearance would have an impact on mortality, but the magnitude of the impact was very uncertain. It commented that it was likely that the upper bound of that magnitude was from the published data sources used by the company. The committee concluded that the true value was likely to lie somewhere in between no benefit and that upper bound, and that the company's base case was likely optimistic.

The mean time since transplant should be used at model entry

3.11 Time since transplant at entry to the model affected both the risk of

mortality and the risk of CMV recurrence. In its base case, the company used the median time since transplant from SOLSTICE to inform the baseline characteristics of the modelled population. It suggested this was reasonable because the mean and median values were not the same and outliers could influence the mean estimate. The ERG preferred to use the mean time since transplant to fully reflect the whole population. The committee was aware that time since transplant had a substantial effect on outcomes and would have preferred to see data on the distribution of this (see section 3.3). In the absence of this information, it agreed at the first meeting that it was more appropriate to use the mean value. In response to consultation, the company agreed, and updated the model. The committee concluded that the updated model was suitable for decision making.

The impact of leukaemia recurrence and graft failure should be included in the economic model

3.12 The committee discussed the inclusion of disease complications in the model:

- The company base case originally did not include recurrences of leukaemia, but the ERG recommended doing this based on NICE's technology appraisal guidance on letermovir for preventing cytomegalovirus disease after a stem cell transplant. At technical engagement, the company did a scenario analysis that included the costs of leukaemia recurrence for 6 months and leukaemia relapse-related mortality. The ERG included this analysis in its base case.

- To estimate the probability of graft failure, the company used estimates from Hakimi et al. (2017), which reported that people with a CMV episode at 6 months or more after transplant have a 5.12% chance of graft failure, compared with 1.69% for people without CMV, over 1 year. After technical engagement, the ERG recommended that the company used graft failure data from OTUS, if the data was used to populate much of the model. The company investigated the events of graft failure in OTUS and noted that the impact of updating the model to include this data was small. The ERG agreed, and in its base case used the data from Hakimi et al.

  The committee agreed at the first meeting that disease complications should be included in the model, and accepted the ERG's approach of modelling recurrences of leukaemia and graft failure. In response to consultation, the company incorporated leukaemia recurrences into its model, but noted that this could lead to double counting of mortality. Graft failure was already captured in its base case. The ERG agreed that the company's approach was in line with the committee's preferences, and the committee concluded that the model was suitable for decision making.

The impact of graft-versus-host disease should be included in the model

3.13 The company base case originally included graft-versus-host disease. The ERG considered that people who have had an HSCT and go on to develop graft-versus-host disease have a higher probability of death, so this complication should be included in the model. The company noted the difficulty in identifying a causal relationship between graft-versus-host disease and CMV from the current literature, but provided a scenario including graft-versus-host disease (without a higher mortality risk). At the first meeting, the committee noted that although a causal relationship could not be identified, the effects on overall mortality could have a large impact on the cost-effectiveness estimates. The company noted that data from OTUS is likely to become available in the future that will provide more information on graft-versus-host disease. The ERG included the company's scenario in its base case. The committee accepted the ERG's approach to including graft-versus-host disease in the model. In response to consultation, the company updated its base case to include graft-versus-host disease. The company also updated

the model to account for time since transplant. The ERG disagreed with the company's estimation of the risk of graft-versus-host disease, noting that this may not differ by CMV status, and provided a scenario to explore this. It also noted that the company did not include the impact of graft-versus-host disease on survival, but given that the stage 1 Markov model now had a shorter time horizon (see section 3.9), the impact on the ICER of excluding this was likely to be small. The committee recognised that although developing graft-versus-host disease has not been directly associated with CMV infection, population data suggests that there is a higher incidence of graft-versus-host disease in people who also have CMV. But the committee was aware that clearing CMV may not lead to a lower risk of developing graft-versus-host disease in the future. On balance, it concluded that the company's approach to modelling graft-versus-host disease by CMV status was likely to be reasonable, but the uncertainty meant that the ERG's scenario was also plausible.

Costs in the economic model

The model should include different intravenous administration costs for first and subsequent administrations

3.14 The company assumed that the daily intravenous (IV) administration cost used for various IATs was equal to an NHS reference cost for complex chemotherapy at first attendance. The ERG had noted this cost should only apply to the first administration of IV IATs, when a central line would be inserted, but that the same line could be used for subsequent administrations so subsequent costs would be lower. The ERG judged that the administration costs applied for IV treatments in the IAT arm had been overestimated in the model. It suggested that a lower reference cost for subsequent elements of a chemotherapy cycle should be used for subsequent administration of IV IATs. It did a scenario analysis that explored the impact of using first and subsequent administration NHS reference costs, and another in which daily administration costs for IV treatments were based on the hourly cost of a critical care nurse. At the first meeting, the committee considered that both approaches were plausible, but that using the first and subsequent IV administration NHS

reference costs would be most appropriate. In response to consultation, the company updated its base case, amending the administration cost to account for the reduced cost of subsequent treatment. The committee concluded that the company's approach was in line with its preferences.

The cost of hospitalisation for people with clinically significant CMV is likely to be higher than for people without clinically significant CMV

3.15 The committee considered whether the hospitalisation costs for people with clinically significant CMV would be different to the costs for those without clinically significant CMV. The company had applied a higher unit hospitalisation cost for clinically significant CMV than for no clinically significant CMV. This was based on weighted average NHS reference costs for a non-elective long stay for infectious diseases with or without interventions. The ERG preferred to apply an equal unit hospitalisation cost for clinically significant CMV and no clinically significant CMV, because it considered that the difference in costs would have already been incorporated into CMV treatment costs in the model. The committee considered that people hospitalised with clinically significant CMV would need extra care and incur greater costs (beyond treatment costs) than people hospitalised without clinically significant CMV. It concluded that the company's approach was appropriate.

Utility values in the economic model

Utilities are appropriately captured in the model

3.16 The ERG originally highlighted concerns about the company's approach to modelling estimated EQ-5D-3L values from the EQ-5D-5L data in SOLSTICE. At technical engagement, the company clarified the multiple imputation method it used. This was based on the approach used in NICE's technology appraisal guidance on letermovir for preventing cytomegalovirus disease after a stem cell transplant. The committee was satisfied with this approach. The ERG also noted that the utility values applied for the stage 2 Markov model were slightly inconsistent with those applied in the stage 1 Markov model. It noted that the values might

underestimate the health-related quality of life of people who did not have clinically significant CMV after SOT, and overestimate the quality of life in people after HSCT. The committee recognised this slight inconsistency, but in the absence of further data considered the utilities used were appropriate.

Cost effectiveness

Because of the uncertainty, an acceptable ICER is around £20,000 per QALY gained

3.17 NICE's guide to the methods of technology appraisal notes that above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. Because of the high level of uncertainty in the clinical and economic evidence, the committee agreed that an acceptable ICER would be around £20,000 per QALY gained.

The cost-effectiveness estimates are uncertain but are likely within the range NICE considers an acceptable use of NHS resources

3.18 The company's updated base-case ICER for maribavir compared with IAT was around £20,000 per QALY gained. This included confidential commercial arrangements for maribavir and the comparators, so the exact ICERs cannot be reported here. The company's base case included the following assumptions, which were preferred by the committee:

- including graft-versus-host disease by CMV status, assuming CMV increases the probability of graft-versus-host disease (section 3.13)
- modelling mortality using the ERG's midpoint scenario, in which people with CMV were arbitrarily assumed to have twice the risk of mortality than people without CMV (section 3.10)

- using the latest OTUS data to estimate the probability of clearance at week 8 (section 3.6).

  The committee considered the uncertainty associated with the cost-effectiveness estimates. But it concluded that the most plausible ICER was around £20,000 per QALY gained.

Innovation

Maribavir is innovative in that it is an oral treatment that can be taken at home, but all of the benefits are captured in the modelling

3.19 The committee agreed that there is an unmet need for an effective and tolerable treatment for CMV infection that is refractory to treatment in adults who have had an SOT or HSCT. It considered that having an oral treatment was innovative and reduced the need for people to be in hospital to receive treatment, but that these benefits were captured in the model.

Equalities

No relevant equalities issues were identified

3.20 The company stated that people from some minority ethnic family backgrounds are more likely to develop comorbidities and therefore would be more likely to need a transplant. They may also wait longer for a suitable organ donor. It also considered that older people have fewer treatment options because of toxicity. Both of these groups can need high levels of immunosuppression and so have an increased risk of CMV infection and graft rejection. Risk of transplant, time to transplant and age at transplant are not issues that can be addressed in a technology appraisal of a treatment for CMV. The company did not investigate whether treatment with maribavir works better in any particular groups. The committee concluded that no equalities issues were identified that could be addressed by this appraisal.

Conclusion

Maribavir is recommended

3.21 The committee recognised that there are limited treatment options for CMV infection that is refractory to treatment and that an oral treatment given at home would be beneficial. It acknowledged that SOLSTICE data suggests that maribavir improves clearance compared with IAT, but the results were highly uncertain. It considered that there was uncertainty in the cost-effectiveness estimates, but that the most likely estimates were within the range NICE usually considers a cost-effective use of NHS resources. So, maribavir is recommended for treating CMV infection that is refractory to treatment in adults who have had a SOT or HSCT.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a person has CMV infection that is refractory to treatment and the doctor responsible for their care thinks that maribavir is the right treatment, it should be available for use, in line with NICE's recommendations.

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.

Victoria Gillis-Elliott and Janet Boadu
Technical leads

Michelle Green
Technical adviser

Kate Moore
Project manager

ISBN: 978-1-4731-4956-4

Accreditation