NICE National Institute for Health and Care Excellence

NICE guidance

Mogamulizumab for previously treated mycosis fungoides and Sézary syndrome

Technology appraisal guidance
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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 Mogamulizumab is recommended, within its marketing authorisation, as an option for treating Sézary syndrome in adults who have had at least 1 systemic treatment. It is recommended only if the company provides mogamulizumab according to the commercial arrangement.

1.2 Mogamulizumab is recommended as an option for treating mycosis fungoides in adults, only if:

- their condition is stage 2B or above and
- they have had at least 2 systemic treatments and
- the company provides mogamulizumab according to the commercial arrangement.

1.3 This recommendation is not intended to affect treatment with mogamulizumab 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

Standard care for previously treated mycosis fungoides or Sézary syndrome includes brentuximab vedotin, methotrexate, bexarotene, peginterferon and chemotherapy.

Mogamulizumab is licensed for treating mycosis fungoides and Sézary syndrome in adults who have had at least 1 systemic treatment. The company has positioned it for Sézary syndrome after 1 or more systemic treatments but only for advanced mycosis fungoides after 2 or more systemic treatments. This is because there are limited treatment options for this population.

Mogamulizumab has not been directly compared with standard care used in the NHS. It has only been directly compared with vorinostat, which is not available in the UK. Indirectly comparing mogamulizumab with evidence from people having standard care in the NHS

suggests that people are likely to live longer with mogamulizumab. The evidence from this indirect comparison is uncertain because all the different factors that affect clinical outcomes may not have been considered. But it is unlikely that the evidence can be improved so the uncertainty is considered acceptable.

Mogamulizumab does not meet NICE's criteria to be considered a life-extending treatment at the end of life. Also, there is uncertainty about the cost-effectiveness evidence, but the cost-effectiveness estimates are likely to be within what NICE normally considers an acceptable use of NHS resources. So, mogamulizumab is recommended.

2 Information about mogamulizumab

Marketing authorisation indication

2.1 Mogamulizumab (Poteligeo, Kyowa Kirin) is indicated for 'the treatment of adult patients with mycosis fungoides or Sézary syndrome who have received at least one prior systemic therapy'.

Dosage in the marketing authorisation

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

Price

2.3 The list price of mogamulizumab is £1,329 per vial containing 4 mg of mogamulizumab per ml (excluding VAT; BNF online, accessed October 2021). The company has a commercial arrangement (simple discount patient access scheme). This makes mogamulizumab 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 Kyowa Kirin, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

Treatment pathway

People with mycosis fungoides or Sézary syndrome would welcome a new treatment option

3.1 Cutaneous T-cell lymphoma is a rare type of non-Hodgkin lymphoma that affects the skin. It includes mycosis fungoides, the most common type, and Sézary syndrome, which is closely related. The clinical experts explained that Sézary syndrome is an aggressive disease and prognosis tends to be poor. Both patient experts described how living with a scaly itching rash all the time significantly affects their health-related quality of life. Sleep is affected. Cracks and open wounds are common, particularly on the hands and feet, which limits the ability to walk and carry out daily activities. The clinical experts explained that the disease particularly affects people's appearance and people sometimes rely on carers to help with daily activities. They confirmed that the treatments recommended in the British Association of Dermatologists and UK Cutaneous Lymphoma Group guidelines on managing primary cutaneous lymphomas after at least 1 systemic treatment were used in clinical practice. These included brentuximab vedotin, methotrexate, bexarotene, peginterferon and chemotherapy. The patient experts said that treatments such as chemotherapy had little benefit but mogamulizumab had a dramatic improvement. Mogamulizumab improved their itching and skin condition, so they could carry out daily activities more easily, and considerably improved their quality of life. The committee concluded that people with mycosis fungoides or Sézary syndrome who have had at least 1 systemic treatment would welcome an additional treatment option.

The company proposes mogamulizumab for a subgroup of the

population covered by the marketing authorisation

3.2 Mogamulizumab is indicated for treating mycosis fungoides or Sézary syndrome after at least 1 systemic treatment (see section 2.1). For the first and second committee meetings, the company proposed mogamulizumab as an option for a subgroup of the population covered by the marketing authorisation; that is, after at least 1 systemic treatment for people with severe disease that has progressed with brentuximab vedotin or if it is not appropriate. Severe disease was defined as stage 2B and above for mycosis fungoides and all stages of Sézary syndrome. Brentuximab vedotin is recommended as an option for severe CD30-positive disease after at least 1 treatment (see NICE's technology appraisal guidance on brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma). The committee understood that mogamulizumab would most likely be used as an option after 1 systemic treatment for CD30-negative disease and after 2 systemic treatments for CD30-positive disease. But it noted that brentuximab could also be used later in the treatment pathway. The clinical experts explained that around 15% to 20% of people have CD30-positive disease. After the appeal, the company further refined the positioning of mogamulizumab for advanced mycosis fungoides to adults who have had 2 or more systemic treatments. It maintained the positioning in Sézary syndrome for adults who have had 1 or more systemic treatments. Few people with Sézary syndrome have CD30-positive disease. So, this positioning means that in both conditions, most people will have had brentuximab vedotin, or it will be unsuitable. The company explained that this is the population with the greatest unmet need because the only treatment options available to them are repeating previous treatments or clinical trials. The clinical experts confirmed that the company's proposed subgroup with severe disease was clinically relevant and that people in this subgroup had limited treatment options. The committee considered that there was a very high unmet need in this population. The committee concluded that the company positioned mogamulizumab for a subgroup of the population covered by the marketing authorisation and it would account for this in its recommendations.

Standard care is the most appropriate comparator

3.3 The company originally submitted cost-effectiveness analyses, which used clinical-effectiveness data comparing mogamulizumab with vorinostat, a treatment that is not licensed or used in the UK (see section 3.4). In its revised base case after technical engagement, the company included the costs of having bexarotene alone for everyone in the standard care arm. This is because it considered it to be the most common NHS treatment for mycosis fungoides and Sézary syndrome. A clinical expert explained that triple therapy with bexarotene, extracorporeal photopheresis and peginterferon is used in clinical practice. But bexarotene alone would not generally be used, particularly for Sézary syndrome, because it was not effective. Another clinical expert suggested that chemotherapy may also be an option for people who were eligible for mogamulizumab. The committee considered that the company's approach may oversimplify a complex treatment pathway. The company also submitted clinical-effectiveness data for standard care from the hospital episode statistics (HES) database, including other relevant treatments in the standard care arm. These included methotrexate, bexarotene, peginterferon and chemotherapy. Overall, the committee concluded that standard care was the most appropriate comparator.

Clinical evidence

There is no trial evidence comparing mogamulizumab with standard care

3.4 The clinical evidence for mogamulizumab came from MAVORIC, a phase 3, open-label, randomised controlled trial. MAVORIC compared mogamulizumab with vorinostat in 372 adults with stage 1B to 4B relapsed or refractory mycosis fungoides or Sézary syndrome. There was no evidence directly comparing mogamulizumab with treatments currently used as NHS standard care (see section 3.3). In NICE's technology appraisal guidance on brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma, the ALCANZA trial was used. It compared brentuximab with the physician's choice of treatment

(methotrexate or bexarotene). The committee understood that:

- An anchored indirect treatment comparison using ALCANZA was not possible because there was no common treatment to connect the 2 trials.
- The population in ALCANZA was different to MAVORIC because people with Sézary syndrome were excluded, everyone had CD30-positive disease, and some had primary cutaneous anaplastic large-cell lymphoma (a subtype of cutaneous T-cell lymphoma).
- There was a high level of crossover in ALCANZA and the company did not have access to individual patient-level data to calculate crossover-adjusted survival estimates for the comparator arm.

The company assumed that vorinostat was a suitable proxy for standard care in the NHS based on:

- similar progression-free survival to the physician's choice arm in ALCANZA
- clinical expert opinion and
- similar response rates to those seen in bexarotene clinical trials.

The ERG explained that if vorinostat and the physician's choice were similar, people in the physician's choice arm in ALCANZA would have longer progression-free survival and overall survival because they had less severe disease. However, overall survival for the physician's choice arm was shorter than with vorinostat. The clinical experts could not comment on vorinostat's clinical effectiveness because it is not available in the UK. However, they emphasised that mogamulizumab had been shown to be effective in delaying disease progression and improving quality of life both in the trial and in their clinical experience. The committee noted that:

- mogamulizumab improved progression-free survival in MAVORIC compared with vorinostat (hazard ratio 0.43, 95% confidence interval 0.31 to 0.58)
- the overall survival estimates were uncertain because MAVORIC was not powered to detect overall survival differences
- 72% of people in the severe disease subgroup crossed over from vorinostat to mogamulizumab, so crossover adjustment was needed (see section 3.9).

Overall, the committee was concerned about using these clinical-effectiveness data because vorinostat was not licensed for use in the UK and did not represent NHS standard care. The committee considered that evidence for the relative effectiveness of mogamulizumab was limited and concluded that evidence from clinical trials, used to estimate the relative treatment effect of mogamulizumab, was highly uncertain compared with NHS standard care.

HES data suggests that mogamulizumab is likely more effective than standard care but the evidence is uncertain

3.5 Real-world data from England's HES database was presented by the company at the first committee meeting and used to support its preferred approach to extrapolating survival for the comparator arm from MAVORIC (see section 3.9). After consultation, the company submitted an unanchored indirect treatment comparison comparing mogamulizumab outcomes from MAVORIC with HES data. The committee noted that, unlike the MAVORIC data (see section 3.4), the HES data did not need any crossover adjustment. The committee noted that NICE's Decision Support Unit technical support document 18 states that all effect modifiers and prognostic factors should be accounted for in an unanchored indirect treatment comparison. This is because 'failure of this assumption leads to an unknown amount of bias' in the comparison. It noted that the MAVORIC data was only matched to the HES data for the proportion of people with mycosis fungoides and Sézary syndrome. Age (a known prognostic factor) and sex (which can potentially affect survival) were not matched. This was because the company considered that these were similar between the MAVORIC and HES data and wanted to avoid reducing the sample size unnecessarily. The ERG explained that age and sex should have been matched and pointed out that differences in mean age increased by 2.5 years after matching. After the appeal, the company submitted a scenario analysis including age and sex, which had a negligible effect on the hazard ratio for overall survival. The hazard ratio for overall survival, adjusted for age and sex, was 0.38 (95% confidence interval 0.25 to 0.59), showing mogamulizumab was associated with an improvement in overall survival compared with standard care. The committee was aware that several additional prognostic factors recognised in the literature and in a study by the

Cutaneous Lymphoma International Consortium included:

- stage of disease
- levels of lactate dehydrogenase and
- large-cell transformation.

However, information on these and other prognostic factors were not available in the HES database and so could not be matched. The company considered that, in the HES database, people having systemic therapy had an Eastern Cooperative Oncology Group (ECOG) stage of 1 or less and adequate haematological, liver and kidney function. But no evidence to support this was provided. The committee noted that there were important limitations to using proxies for the stage and the duration of disease. Overall, the committee recognised that the HES analysis addressed some of the issues with the original submission and commended the company on its efforts. But the limitations of the data and the lack of information on prognostic factors meant that the indirect analysis results were uncertain. The committee considered that although there were uncertainties in the indirect comparison it was unlikely that these could have been addressed. The committee concluded that the indirect comparison suggested that mogamulizumab was more effective than standard care but that the evidence was uncertain.

The MAVORIC subgroup with severe disease is clinically relevant but the results create uncertainty

3.6 The company used clinical-effectiveness data from a post-hoc subgroup of 287 people with severe disease in MAVORIC to reflect its proposed positioning (see section 3.2). The committee recalled that severe disease was considered a clinically relevant subgroup. But it noted that in this subgroup, it could not easily determine the proportion of people who had disease progression after brentuximab vedotin (CD30-positive disease) and those not eligible for brentuximab vedotin (CD30-negative disease). It was also concerned that the clinical-effectiveness data included people at different stages in the treatment pathway and did not differentiate between mycosis fungoides and Sézary syndrome. It considered that this may not be appropriate given the differences in expected survival between the conditions. The committee would have

liked to have seen separate analyses by disease type and line of treatment. It recalled that all analyses used vorinostat as a comparator, which did not represent NHS standard care (see section 3.4). After the appeal, the company reweighted the MAVORIC trial data to match the characteristics of the subgroup of the population covered by the marketing authorisation, as observed in the HES data. Based on the evidence, the committee concluded that the MAVORIC subgroup with severe disease was clinically relevant. But using a mixed population, which grouped several lines of treatment together, created uncertainty. Also, MAVORIC did not compare mogamulizumab with a relevant comparator.

Economic model

The company's model structure is acceptable

3.7 In the company's partitioned survival model, 3 different treatment pathways were modelled:

- people who did not have an allogeneic stem cell transplant
- people who had an allogeneic stem cell transplant after current treatment (that is, mogamulizumab or standard care)
- people who had an allogeneic stem cell transplant after subsequent treatment.

The company initially used clinical expert advice to estimate the proportion of people having an allogeneic stem cell transplant after current treatment because this was not allowed in MAVORIC. After consultation, the company used HES data (see section 3.5) for this proportion. The committee was aware that the estimated treatment effect in MAVORIC may have differed if allogeneic stem cell transplant had been allowed. It recognised that some people may have an allogeneic stem cell transplant in clinical practice. But in the model, it preferred removing allogeneic stem cell transplant after current treatment, to avoid double-counting survival benefit in MAVORIC and to reduce potential bias. After the appeal, the company excluded allogeneic stem cell transplant after current treatment. The company noted that by doing this, the standard care arm included some of the benefits of allogeneic stem cell transplant but

none of the costs. The committee considered that the cost-effectiveness estimates might have been lower if the costs of allogeneic stem cell transplant after current treatment were included in the submission. It understood that this had a small effect on the cost-effectiveness estimates. The committee concluded that the company's economic model structure was acceptable and that allogeneic stem cell transplant after current treatment should be excluded from the model.

The comparative evidence from MAVORIC for time on treatment and next-treatment free survival is appropriate for decision making

3.8 The company originally modelled standard care using MAVORIC clinical-effectiveness data because it considered that vorinostat could be used as a proxy for standard care (see section 3.4). In its revised base case after technical engagement, the company preferred to use the costs of bexarotene alone for 48 weeks to represent the likely costs for people who have NHS standard care. After consultation, the company reverted to the ERG's preferred assumption of using the time on treatment for vorinostat and for relevant standard care treatments. In addition, clinical-effectiveness data for the standard care arm was updated to reflect data from the HES analysis (see section 3.5). After the appeal, the company estimated next-treatment-free survival and time on treatment for both arms from the reweighted MAVORIC trial, focusing on the refined population. The committee heard that the ERG agreed with the company's choice of distribution for next-treatment-free survival and using Kaplan–Meier curves to estimate time on treatment. Despite the limitations in the data sources, the committee concluded that the data was the most appropriate for decision making.

Overall survival

The exponential curve for both arms is acceptable for decision making

3.9 In MAVORIC, 72% of people in the severe subgroup crossed over from vorinostat to mogamulizumab after disease progression. Therefore,

overall survival in the vorinostat arm was heavily confounded. The ERG and company agreed that an adjustment was needed to estimate what would have happened in the comparator arm if there was no crossover. In the first 2 committee meetings, the company preferred to use the inverse probability of censoring weights (IPCW) method and the ERG preferred a 2-stage estimation method to adjust for crossover. Alongside the company's preferred IPCW crossover adjustment, it chose a log-normal curve to extrapolate overall survival in the mogamulizumab arm and applied an exponential curve to the standard care arm. The ERG preferred the exponential curve for both treatment arms. The committee preferred the ERG's approach and agreed that the company would need to make a strong case to justify using different parametric curves in each treatment arm. After the appeal, the company estimated overall survival for the mogamulizumab arm from the reweighted MAVORIC trial. The company and ERG agreed that the exponential extrapolation in the mogamulizumab arm was the best fitting curve and was clinically plausible. The company also updated the data source for overall survival in the standard care arm to the HES data after the appeal. The company chose the exponential extrapolation to estimate overall survival in the standard care arm. The company explained that although the generalised gamma was the best fitting curve, it did not consider the extrapolation to be clinically plausible because it predicted a plateau in survival. The ERG noted that the exponential extrapolation was the best fitting curve for the mogamulizumab arm but the worst fitting curve for the standard care arm. So, the ERG preferred the log-normal extrapolation because it was the second-best fitting extrapolation. The log-normal curve showed that 10% of people who had standard care would be alive at 10 years. The clinical experts explained that only people who had allogeneic stem cell transplants would be alive at 10 years. The clinical experts added that people whose disease progresses and need second- and third-line treatments do not have a good prognosis and would not be long-term survivors. The committee agreed with the company and clinical experts that because the modelling did not include people who have had allogeneic stem cell transplant, the log-normal curve was not clinically plausible. The committee concluded that the company and ERG's preferred exponential curve for the mogamulizumab arm and the company's preferred exponential curve for the standard care arm were acceptable for decision making.

A 2-year stopping rule is not appropriate

3.10 The company included a 2-year stopping rule for mogamulizumab in its revised base case. There was no evidence to support a stopping rule because it was not included in either the summary of product characteristics or the MAVORIC trial. The committee understood that the estimated treatment effect could have differed if a stopping rule had been used. The company suggested that the treatment effect was unlikely to differ substantially because in MAVORIC, only a small proportion of people had mogamulizumab after 2 years (the data is confidential and cannot be reported here). The committee recalled that it was not convinced that there would be a prolonged treatment benefit after stopping treatment. Before technical engagement, 1 clinical expert suggested that a 2-year stopping rule would not be appropriate if people were still benefitting from treatment. At the committee meeting, the clinical experts explained that treatment would not normally be stopped if it was tolerated and there was an ongoing clinical benefit. The patient experts said they would feel distressed if mogamulizumab was stopped at 2 years, leaving them without any effective treatment options. The committee concluded that a 2-year stopping rule was not appropriate.

Utility values

There may be an effect on carers' health-related quality of life, but this cannot be robustly modelled

3.11 The committee recalled that people with this condition sometimes rely on help from informal carers (see section 3.1). The committee noted that some people would have help from district nurses (for example, with wound dressing). Also, costs for community-based care including home visits, skin and wound care and dressings were included in the model. In the first and second committee meetings, the company's base case modelled the effect of caring on the health-related quality of life of carers by applying an additional utility gain of 0.19 when a person is in the disease control health state. This was the difference between the direct estimates of carer's health-related quality of life when caring for someone in the disease control (0.56) and subsequent treatment states

(0.37) from the company's vignette study. Therefore, only the additional time a person spent in the disease control state after having mogamulizumab compared with standard care contributed to improving carer's health-related quality of life. After consultation, the company submitted 2 scenarios for carer utilities, in which:

- the difference between carer utilities for the disease control and subsequent treatment health states was the same as the difference seen for the people in the trial (0.09)
- absolute values for disease control and subsequent treatment states were used to show that the base case reflected a conservative approach.
- The committee considered that the company's approach was not robust because the utility gain in the base case for carers was implausibly large compared with the expected utility gain for people with the condition. It recognised that there was a lack of detailed methodology on how to model carer utility. But it noted that the company used vignettes in the general population and it was not in line with NICE's guide to the methods of technology appraisal, which states that the EQ-5D is the preferred measure of health-related quality of life in adults. The committee also did not consider it acceptable that the difference between carer utilities for the disease control and subsequent treatment health states would be the same as the difference seen for the people with the disease in the trial. This was because this was an unvalidated assumption, with no supporting evidence. Overall, the committee was not convinced that the company's approach to modelling carer utility values was appropriate. So it preferred to remove them from the base-case analysis, but recognised the burden placed on some carers. After the appeal, the company excluded carer utilities from its base-case analysis. Because the committee had recognised that there was a burden on some carers, the appeal panel considered that it must be clear how carer utilities were included in the decision making. The committee considered that including carer utilities in the modelling would have improved the cost-effectiveness estimates. Because it was not possible to robustly model them in this appraisal, the committee concluded it would consider them qualitatively in its decision making.

End of life

Mogamulizumab is not considered to be a life-extending treatment at the end of life

3.12 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. At the first meeting, using MAVORIC data with the company's preferences, the model predicted a median survival of 21 months and a mean survival of 37 months in the standard care arm. The committee's preferred assumptions predicted a mean survival of between 33 months and 59 months in the standard care arm depending on if an IPCW or 2-stage estimation crossover adjustment was used. The company also submitted HES data, which showed a median overall survival of around 1.3 years for people who have had 1 treatment. After consultation, the company submitted an updated HES analysis (see section 3.5) and considered that the end of life criteria had been met. The committee recognised that median life expectancy based on the new HES analysis (17.83 months) was less than 24 months. However, it noted that the mean extrapolated discounted and undiscounted life years in the standard care arm of the cost-effectiveness model based on the HES data, were 2.87 and 3.31 years respectively. The committee also considered a study by the Cutaneous Lymphoma International Consortium and the professional organisations' responses to technical engagement. After the appeal, the committee reconsidered this data and noted that the median data from the Cutaneous Lymphoma International Consortium study and the professional organisations' responses to technical engagement referred to time from diagnosis, rather than time from eligibility for second-line treatment. The committee acknowledged that time from eligibility for second-line treatment was the relevant period that should have been considered. After the appeal, the company updated the data source for overall survival in the standard care arm to the HES data. In the refined population, the HES data showed that median overall survival from time from eligibility for second-line treatment was 13 months but when the HES data was used in the model, it showed that mean overall survival was 28 months, when the exponential curve was chosen for both treatment arms. The committee

noted that all other extrapolations of the HES data in the model led to a mean life expectancy greater than 28 months. The committee remained concerned about the differences between the median overall survival results from the HES analysis and the mean results produced when it was used in the model. The company considered that the mean was skewed by the long survival of around 10% of people having allogeneic stem cell transplant after current and subsequent treatments in the HES dataset. The ERG noted that people who had allogeneic stem cell transplant were part of the same cohort for which life expectancy was estimated, so their long survival does not bias life expectancy. The clinical experts explained that the life expectancy of people with the condition is variable and both the mean and median figures could be plausible. The committee recalled that cost-effectiveness results and decisions are based on mean quality-adjusted life years (QALYs) and costs. So, the committee still considered that the best estimate of expected survival came from modelling mean life expectancy. The committee noted that NICE's guide to the methods of technology appraisal states that the appraisal committee must be satisfied that:

- the assumptions used in the reference case economic modelling are plausible, objective and robust and
- the estimates of the extension to life are sufficiently robust.

Overall, the committee was not convinced there was robust evidence that the short life-expectancy criterion had been met. It concluded that mogamulizumab could not be considered a life-extending treatment at the end of life.

Cost-effectiveness estimates

An acceptable ICER is towards the upper end of the range normally considered cost effective

3.13 NICE's guide to the methods of technology appraisal notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per 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. The committee noted the high level of uncertainty associated with the MAVORIC analysis, specifically:

- The relative treatment effect of mogamulizumab compared with NHS standard care was uncertain because MAVORIC did not include the most appropriate comparator for NHS standard care (see section 3.4).
- The company's preferred subgroup was limited because it included a mixed population in a single post-hoc analysis (see section 3.6).

But it acknowledged that the HES analysis addressed some of the issues associated with MAVORIC (for example, comparator and crossover adjustment), and the rarity of the conditions means it would be hard to collect further data to reduce the uncertainty. It also recalled that including carer utilities and the costs of allogeneic stem cell transplant in the standard care arm would likely decrease the ICER. The committee noted that considering carer utilities and the costs of allogeneic stem cell transplant in the standard care arm would offset some uncertainty around the cost-effectiveness analyses. The committee therefore agreed that an ICER towards the upper end of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained) would be acceptable.

The cost-effectiveness estimates are uncertain but are within the range normally considered cost effective

3.14 After the appeal, the company's updated base-case ICER for mogamulizumab compared with standard care was £28,233 per QALY gained, including the commercial arrangement for mogamulizumab. Adjusting the baseline characteristics of the MAVORIC trial to match the refined population had a minimal impact on the ICER. The committee understood that there was a small effect on the ICERs when including the commercial arrangement for bexarotene but the exact data is confidential so cannot be reported here. The committee considered the company's base case suitable for decision making. The company's base case included:

- clinical-effectiveness data for overall survival for standard care from the unanchored indirect comparison using real-world data from the HES analysis and reweighted MAVORIC data
- the exponential curve to extrapolate overall survival for mogamulizumab and standard care
- allogeneic stem cell transplant excluded after current treatment.

The company's base case excluded carer health-related quality of life. The committee considered the substantial uncertainty in all the cost-effectiveness estimates when applied in an NHS setting but noted the rarity of the cancer being appraised. The committee agreed that, based on its preferred assumptions, the most plausible ICER was within the range it considered acceptable for this appraisal (see section 3.13). The committee concluded that mogamulizumab was cost effective for advanced mycosis fungoides after at least 2 previous systemic treatments and for Sézary syndrome after at least 1 previous systemic treatment.

Innovation

Benefits not captured in the model are considered in the committee's decision making

3.15 The company considered mogamulizumab to be innovative because there are limited effective treatment options for people with advanced mycosis fungoides after at least 2 previous systemic treatments and for people with Sézary syndrome after at least 1 previous systemic treatment. The company emphasised the importance of improved health-related quality of life for these conditions, which cause lesions that affect people's appearance. The committee recalled this, the reported benefits in improving symptoms and the burden on carers. The committee also noted that the benefits of allogeneic stem cell transplant in the standard care arm were included in the modelling, but the associated costs were not. So, the committee was willing to qualitatively consider these factors. It also noted that mogamulizumab has an innovative mechanism of action. The committee concluded that mogamulizumab is innovative and the relevant benefits associated with mogamulizumab that were not

captured in the modelling were considered qualitatively in determining an acceptable ICER (see section 3.13).

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 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 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.

4.4 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 patient has advanced mycosis fungoides or Sézary syndrome, and the doctor responsible for their care thinks that mogamulizumab 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.

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