NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Epcoritamab for treating relapsed or refractory follicular lymphoma after 2 or more lines of systemic treatment

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

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

The evaluation 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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: September 2025

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using epcoritamab in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 22 October 2025
- Second evaluation committee meeting: 9 December 2025
- Details of the evaluation committee are given in section 4.

1 Recommendations

1.1 Epcoritamab should not be used to treat relapsed or refractory follicular lymphoma in adults after 2 or more lines of systemic treatment.

1.2 This recommendation is not intended to affect treatment with epcoritamab 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 healthcare professional consider it appropriate to stop.

What this means in practice

Epcoritamab is not required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because there is not enough evidence to determine whether epcoritamab is value for money in this population.

Why the committee made these recommendations

Usual treatment for relapsed or refractory follicular lymphoma after 2 or more lines of systemic treatment includes various combinations of chemotherapy and rituximab-based treatment.

There is an ongoing clinical trial that does not compare epcoritamab with any other treatments. Indirect comparisons suggest that epcoritamab increases how long people have before their condition gets worse and how long people live compared with usual treatment. But these results are uncertain because the epcoritamab and usual treatment studies were designed differently and included different populations.

The economic model is also uncertain because of the assumptions used to model usual treatment.

Because of the uncertainties in the economic model and clinical evidence it is not possible to determine the most likely cost-effectiveness estimates for epcoritamab. So, epcoritamab should not be used.

2 Information about epcoritamab

Marketing authorisation indication

2.1 Epcoritamab (Tepkinly, AbbVie) is indicated for 'the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy'.

Dosage in the marketing authorisation

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

Price

2.3 The list price of epcoritamab is £547.33 for 4 mg/0.8 ml concentrate for solution for injection vials and £6,568.00 for 48 mg/0.8 ml solution for injection vials (excluding VAT; BNF online accessed September 2025).

2.4 The company has a commercial arrangement. This makes epcoritamab available to the NHS with a discount and it would have also applied to this indication if epcoritamab had been recommended. The size of the discount is commercial in confidence.

Carbon Reduction Plan

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for AbbVie will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by AbbVie, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence. In its

submission, the company restricted the population to after 3 or more lines of systemic therapy (fourth line or later). So, some of the committee conclusions outlined in this section are related to this restricted population and not the full marketing authorisation population.

The condition

Follicular lymphoma

3.1 Lymphomas are cancers of the lymphatic system, which is a part of the immune system. Follicular lymphoma is a slow-growing, low-grade lymphoma that affects B lymphocytes. It is the most common type of low-grade lymphoma. People with this condition typically present with painless lumps (enlarged lymph nodes) in the neck, armpit or groin. Some people may have additional symptoms such as night sweats and recurrent fevers. Some people do not have symptoms so the cancer may have advanced by the time it is diagnosed. Follicular lymphomas are commonly staged from stage 1 (best prognosis) to stage 4 (worse prognosis). The staging depends on how many groups of lymph nodes are affected and where they are in the body, the size of the areas of lymphoma and whether other organs outside of the lymphatic system such as the bone marrow or liver are affected. In England in 2022 there were 2,404 diagnoses of follicular lymphoma (1,217 in females and 1,187 in males). The 5-year survival rate for people diagnosed with follicular lymphoma is around 90%. But this is likely to be lower for people with additional risk factors or whose cancer has relapsed or is refractory after previous treatment. Follicular lymphoma has a high risk of relapse or becoming refractory (when the cancer returns or stops responding to treatment). Once people have cancer that is refractory to multiple lines of treatment, follicular lymphoma is no longer considered slow growing. The patient experts explained that follicular lymphoma is not curable which has a profound emotional impact. The most common fear is that the cancer will return or transform into a more aggressive form, and that there will be no remaining treatment options. People with follicular lymphoma described this as a slow torture because

they know treatments will stop working and the cancer will return at some point. Also, because the cancer is defined as low grade, people feel isolated and misunderstood despite the huge emotional burden of having an incurable cancer. The patient experts also highlighted the significant impact on carers because of anxiety, feeling helpless and the daily support given to people with follicular lymphoma. During the committee meeting, a patient expert described their personal experience of follicular lymphoma. They explained their cancer had relapsed 3 times since diagnosis in 2015. They have had several treatments and expressed anxiety that they will eventually run out of treatments, as would many other people. The patient experts outlined how heterogeneous the course of follicular lymphoma is because some people are diagnosed, have treatment and live to a normal age. But approximately 20% or people have aggressive disease that keeps coming back and requires multiple treatments. The patient expert described the profound psychological impact of the repeated relapses. The committee recalled the first-hand experiences shared by people with follicular lymphoma. It concluded that the condition is progressive and incurable, and substantially impacts people in many different ways. It also noted the substantial burden on the families and carers of people with the condition.

Clinical management

Treatment options

3.2 The company explained that when follicular lymphoma is relapsed and non-refractory, third-line treatment options include rituximab plus chemotherapy (with or without rituximab maintenance), or lenalidomide plus rituximab. When follicular lymphoma is relapsed and refractory, third-line treatment options include lenalidomide plus rituximab or obinutuzumab plus bendamustine (with or without obinutuzumab maintenance). Fourth-line treatments include rituximab plus chemotherapy, lenalidomide plus rituximab, chemotherapy or best supportive care. The patient experts explained that current treatments

such as chemotherapy can have many side effects and cumulative toxicity. They highlighted an unmet need for more accessible and better tolerated treatments. They also explained that more treatments are needed because for some people most treatments will be used and exhausted at some point, so another treatment being available will provide a crucial treatment option. This will also support more individualised long-term care. Patient experts also noted clear advantages of epcoritamab over current treatments, including simpler administration because it is given subcutaneously. They also thought that fewer side effects would be expected compared with current treatment, but noted that further evidence would be needed for confidence in the use of epcoritamab to increase. A patient expert who had epcoritamab explained how easy the treatment was and how they were able to continue working during treatment. The clinical experts highlighted that current treatment at fourth line in the UK is very limited, especially for people whose condition was diagnosed at a young age. This is because, by definition, it will be refractory to previous treatments. This means most available treatments have already been used and worked for a while, but stopped working by fourth line. They estimated that less than 25% of people with follicular lymphoma will have third-line treatments or later. The clinical experts outlined that third-line treatment is based on chemotherapy with other treatments or rituximab with other treatments. They explained that treatment options at fourth line will depend on what has been used previously, so there is no single specific comparator. The company did not include best supportive care in its base case. It explained this was because it is expected that people who would have best supportive care would not be considered fit enough to be eligible for an active intervention such as epcoritamab. It also noted that UK clinical experts it consulted confirmed the company's summary of treatments and omission of best supportive care as generalisable to the UK. The EAG disagreed, noting that it received clinical advice that some people not fit enough for chemotherapy would be eligible for epcoritamab. But the EAG did not raise this as a key issue. The committee noted that

treatment options for relapsed or refractory follicular lymphoma at third line or later were varied combinations of 2 chemotherapies and rituximab as base treatments. It understood that treatment lines were not strictly defined with variations on previously used treatments used at later lines. And that it was appropriate to consider a basket comparator that represents the heterogenous population that has these treatments. It also noted there was an unmet need for treatment options at fourth line because a notable proportion of people will have very limited options at this stage. The committee concluded that the company's treatment pathway was appropriate and that it had modelled appropriate comparator treatments at fourth line or later, which included not modelling best supportive care.

Treatment positioning of epcoritamab

3.3 The marketing authorisation for epcoritamab specifies the line of treatment as 'after 2 or more lines of systemic therapy' (third line or later; see section 2.1). However, the company decided to restrict the population to after 3 or more lines of systemic treatment (fourth line or later) in its submitted model. It explained the restriction was to allow it to focus on the population with the greatest clinical unmet need and for whom there are limited treatment options. The EAG clinical experts advised that there is a greater unmet need for epcoritamab at third line. This is because most people will have already had a rituximab combination treatment and bendamustine (an option with obinutuzumab) would not be desirable because of how it affects T-cell function and thus the efficacy of other treatments. So, the EAG supported considering the broader population that included third-line treatment. At the first committee meeting, the clinical experts explained that epcoritamab showed clinical effectiveness in achieving disease response and extending survival at third line or later and fourth line or later, but is more effective at earlier lines. They said there is strong unmet need for both populations. But the main challenge is showing comparative effectiveness at third line against available treatments. This is because comparator trials typically include lines of

treatment used earlier than third line. The clinical experts also advised that defining the population eligible for treatment at fourth line may be difficult because of the variability in earlier treatments. The committee understood that the company could choose to restrict the population in its submission. But it also considered its objective, which is to evaluate a technology in its full marketing authorisation. The committee concluded that this very important issue had not been explored in enough detail. It understood the arguments raised against modelling third-line treatments, but it considered these to be insufficient and not based on a lack of available evidence. The committee noted that there may be more suitable clinical evidence at the third treatment line from registries and trials. So, it considered that restricting the evidence presented to the fourth treatment line or later increased the uncertainty by limiting the clinical data. The committee concluded that it would like to see cost-effectiveness modelling for the full marketing authorisation population (to include people having third-line treatment). It noted that a full justification, including a full breakdown of available evidence, and clear definition of the fourth line or later population would be needed should this modelling still not be possible.

Clinical effectiveness

EPCORE NHL-1

3.4 EPCORE NHL-1 is an open-label, single-arm phase 1 and 2 trial investigating epcoritamab in people with diffuse large B-cell lymphoma, follicular lymphoma or mantle cell lymphoma after at least 2 previous treatments. It started in June 2020 and is currently ongoing. The study included dose-escalation, dose-expansion and dose-optimisation phases. The main evidence included in the company submission was from the follicular lymphoma dose-expansion cohort, restricted to after 3 or more treatments (fourth line or later). People had 48 mg of epcoritamab once weekly. This cohort included 81 people, but the number of UK participants is confidential. The EAG had some concerns with data validation because

some information shared by the company could not be validated. This included some adverse event data and trial data for third-line treatment. It also expressed concerns with generalisability of the trial data to the UK. This was because of the small sample and differences in the ages, sex and family background of participants to the UK population (specific characteristics are confidential and cannot be reported here). But it noted that the EAG's clinical experts did not raise concerns with generalisability. The EAG also raised concerns with the censoring of COVID-19 deaths in the clinical-effectiveness data (see section 3.6). The company explained that clinical experts it consulted also thought the trial baseline characteristics generalisable to the UK. And that the trial results were reflected in outcomes seen in clinical practice. The results of the trial cannot be reported here because the company presented data that it considered confidential. During the committee meeting, the company explained that longer follow-up data was available for the dose-optimisation cohort. But this information was not shared in time for the committee meeting. The committee concluded that the EPCORE NHL-1 trial data was suitable for decision-making. But it noted the data was limited by being from a single arm trial instead of a randomised trial. It understood that longer follow-up data was recently made available for the dose-optimisation cohort. So, it concluded that it would like to see this data.

Comparator data

3.5 The company did a systematic literature review to identify relevant clinical evidence for treatments for relapsed or refractory follicular lymphoma at fourth line and after. This was done to generate comparative evidence for epcoritamab and comparator treatments because EPCORE NHL-1 is a single-arm trial. The company identified 3 studies but deemed that none were suitable for generating comparative effectiveness data with epcoritamab because of generalisability concerns (either with the population characteristics or treatments used in the study). So, the company worked with the Haematological Malignancy Research Network

(HMRN) to identify suitable data. The HMRN is an ongoing population-based cohort consisting of data for UK patients with a haematological malignancy or related precursor condition. The HMRN covers the Yorkshire and Humber and Yorkshire Coast regions. The HMRN data shared by the company was retrospective observational data for adults with relapsed or refractory follicular lymphoma and starting treatment at fourth line or later. The EAG raised concerns with using the HMRN data alongside EPCORE NHL-1 data to generate comparative evidence. This is because of the following differences between the 2 data sources:

- study design (phase 1 and 2, open-label clinical trial versus retrospective observational dataset)
- years of conduct, sample size and median follow-up (figures are confidential and cannot be reported here)
- inclusion criteria (the HMRN dataset was not specific for relapsed or refractory follicular lymphoma)
- baseline characteristics, including treatment effect modifiers such as previous treatments, and lack of reporting in HMRN on race, ethnicity, body mass index, and renal and hepatic function.

The EAG was unable to identify suitable alternative data for comparators at fourth line or later. But it noted suitable data may be available for comparators at third line or later. Experts consulted by the EAG had suggested that the company might be able to extract third-line data from the HMRN dataset. The company said this might be possible but it had not explored this in detail. The committee asked clinical experts for their views on the suitability of alternative comparator data to the HMRN. The SCHOLAR-5 trial included chemotherapy-based treatments, rituximab-based treatments, experimental treatments and stem cell transplants. But the clinical experts noted that the company for epcoritamab would not have access to the trial data and data at fourth line was not published. They also explained that the LEO cohort was exclusive to cancer centres in the US and used treatments that were not available in the UK, so it is

not generalisable to the UK. The ReCORD-FL study included chemotherapy-based treatments, rituximab-based treatments and stem cell transplants. But clinical experts noted it did not include progression-free survival outcomes, which are important for modelling. During the committee meeting, the clinical experts identified other studies, including the FOUNDATION UK and REFRACT trials. They expected these trials to produce very useful data, but the outcomes would not be available for some time. The clinical experts thought that the HMRN data was very generalisable to the rest of the UK. They noted some differences in age and sex to the UK population but thought these differences would bias results in a small way in opposite directions that would cancel out any meaningful differences. They understood that the HMRN data covered a long time period but did not expect older data on older treatments to be much different from data on treatments used today. And they expected any adjustments needed to account for any differences would be minor. The committee understood the views of clinical experts, but it noted that the HMRN data might include time periods before rituximab was routinely available in the UK. It noted that the intention of fourth line treatment may have changed over time as different treatments became available. The committee considered that there were potential inconsistencies between alternative sources of comparator data and the HMRN dataset that required further exploration. It also thought that data for use of comparators as a third-line treatment could also be explored (see section 3.3). It concluded that a full assessment of feasibility for all available comparator data should be explored within scenario analyses and this data should be used to validate model outcomes. It also concluded that a more complete assessment of generalisability should be provided for all analyses.

Adjusting survival data for COVID-19 deaths

3.6 The EPCORE NHL-1 trial started in June 2020 and was impacted by the COVID-19 pandemic. The company reported that excess mortality was observed in the trial and clinical review identified a confidential number of

COVID-19-attributable deaths. A proportion of these people had achieved complete response before death, so the company considered the condition would not have progressed in these people had they survived. So, these deaths were censored by the company in survival outcomes used in its submission. The company thought this approach was consistent with the HMRN dataset because this reported no deaths from COVID-19. The EAG raised concerns with the censoring of COVID-19 deaths in the EPCORE NHL-1 data. It explained that EAG's clinical experts thought the COVID-19-adjusted survival data too optimistic. Also, it noted that the HMRN dataset was also likely impacted by the COVID-19 pandemic. It understood the company reported that no deaths were observed in the HMRN data, but the EAG had not seen sufficient evidence to confirm this. The EAG further highlighted uncertainty with determining whether COVID-19 was the sole cause for a person's death, or merely present during a death caused by other reasons. As a result, the EAG decided to use the EPCORE NHL-1 survival data that was not adjusted for COVID-19 deaths. During the committee meeting, the company explained that it could not censor COVID-19 deaths in the HMRN data because there were no deaths. The clinical experts explained that the COVID-19 pandemic caused a distinct increase in mortality in people with follicular lymphoma of about 15%. They explained that recently published evidence showed survival before and after the COVID-19 pandemic was very similar to that in the trial. And that the number of COVID-19 infections have significantly reduced in the latest trial data for the dose-optimisation cohort. The clinical experts highlighted that COVID-19 was the sole reason for the observed increase in mortality and must be accounted for in the clinical evidence. The committee agreed that in principle the impact of COVID-19 should be accounted for in the EPCORE NHL-1 clinical evidence. But it considered that the change in outcomes from censoring COVID-19 deaths was an optimistic approach. It also noted the cost-effectiveness results were very sensitive to COVID-19 censoring. The committee concluded that the company had not sufficiently

explored alternative options for accounting for COVID-19 deaths, considering this is such an important issue. So, it would like to see more complex methods for accounting for COVID-19 deaths, instead of only censoring them, such as using causal inference.

Indirect treatment comparison

3.7 To generate comparative evidence for epcoritamab and current treatments at fourth line or later for relapsed or refractory follicular lymphoma, the company did an unanchored matching adjusted indirect comparison. This involved reweighting EPCORE NHL-1 data to match characteristics of HMRN data for relevant treatment effect modifiers and prognostic variables. Specifically, the data were adjusted so the cohorts had the same proportions of people for the following variables:

- aged 60 years or over
- male
- disease stages 3 to 4
- previous autologous stem cell transplant
- previous chimeric antigen receptor T-cell (CAR-T) therapy
- disease progression within 24 months of first-line treatment
- disease refractory to most recent treatment
- disease refractory to both anti-CD20 and alkylator treatments
- 4 or more previous lines of treatment
- previous treatment with lenalidomide plus rituximab.

These adjustments reduced the effective sample size of the EPCORE NHL-1 cohort from 81 to 40 people. The analysis produced progression-free survival, overall survival, objective response rate and complete response outcomes for epcoritamab and current treatments. The results are confidential and cannot be reported here. But the outcomes for epcoritamab were better with the matching adjusted indirect comparison. The EAG had concerns with the indirect comparison. First, the effective sample size for the indirect comparison was small and likely

biases results. Second, strict trial selection criteria means the indirect comparison is unlikely to account for differences in the trial and real-world populations. Third, the indirect comparison produces unexpected results compared with unadjusted data because survival with epcoritamab improved (the results are confidential and cannot be reported here). Fourth, it noted that the Eastern Cooperative Oncology Group (ECOG) and Follicular Lymphoma International Prognostic Index (FLIPI) scores were not adjusted for in the analysis but are considered key prognostic factors. The company explained that ECOG and FLIPI scores were not included because they were only available in the HMRN data at baseline and not over time. The clinical experts noted that these were important prognostic factors, but research has shown that age and sex were the most important prognostic factors, especially at fourth line. Because these 2 variables were included in the indirect comparison, the clinical experts were not concerned. The clinical experts also explained why the survival outcomes for epcoritamab improved when adjusted in the indirect comparison. They pointed out that the EPCORE NHL-1 population was older, had more refractory disease and had more previous treatments than other populations. This was to reflect a higher-risk population with no treatment options. But this meant that adjusting the epcoritamab population to match the HMRN population excluded people at higher risk and weighted down the overall risk of the epcoritamab population. The company thought that the overall fitness of the EPCORE NHL-1 population was worse than the HMRN population. The committee asked the company whether it did a simulated treatment comparison. The company explained that it did not do this because this analysis relies on a large number of events, which were not present in the small sample. The committee concluded that the company's technical approach to the indirect treatment comparison was appropriate. But it noted that a simulated treatment comparison may be possible and it would like to see this analysis to validate the matching adjusted indirect treatment comparison. It further noted uncertainty with the choice of comparator

data as outlined in section 3.5. So, in line with its conclusions on comparator data, the committee would like to see updated indirect comparisons using alternative comparator data sources. The committee concluded that sufficient evidence had not been provided to understand the differences between the EPCORE NHL-1 and HMRN database populations. Also that prognostic factors had not been fully explored, especially prognostic factors for people with refractory disease.

Economic model

Company's modelling approach

3.8 The company built a partitioned survival model with a weekly cycle length and a 35.2-year time horizon to compare the cost effectiveness of epcoritamab with current treatments at fourth line or later. The model included 3 health states: progression free, progressed disease, and death. People were modelled to start in the progression-free health state until disease progression or death. People with progressed disease remained in this health state until death. Background mortality was used in the model to ensure that the modelled survival did not exceed the survival of an age- and sex-matched population within the UK. The company modelled the comparator as a basket of current treatments at fourth line or later. The basket was weighted based on relative use of each treatment based on HMRN data. This data is confidential and cannot be reported here. People were modelled to stop epcoritamab treatment because of progression or other reasons and a 3-year stopping rule was applied to people reaching complete response. Treatment discontinuation for comparator treatments was obtained directly from HMRN data reflecting the impact of the varied durations of different treatments. The company did not apply treatment waning in the model. The committee concluded that the company's model was appropriate for decision making.

Modelling of comparator efficacy

3.9 The company generated overall survival and progression-free survival curves by fitting log-normal curves to the EPCORE NHL-1 data adjusted to the HMRN dataset through the matching adjusted indirect comparison. Hazard ratios from the indirect comparison were applied to the unadjusted epcoritamab data to obtain the overall survival and progression-free survival outcomes for current treatment at fourth line or later. The company explained that using adjusted, rather than unadjusted, epcoritamab data would have been more uncertain because of the reduced sample size. And that using the unadjusted data was also consistent with how other inputs were obtained in the model. The company also explained that it assumed hazards were proportional because no treatment waning was included. But, it included background mortality. The EAG agreed with the use of proportional hazards for the period in which trial data was available. It was not sure this was appropriate for efficacy data extrapolated into the future. However, given the concerns the EAG identified with the indirect treatment comparison (see section 3.7), it preferred to use HMRN data directly in its base case to model efficacy for treatment at fourth line or later. This naive comparison was with a log-normal extrapolation for overall and progression-free survival. The EAG considered that its approach closely matched the overall survival Kaplan–Meier data from the HMRN dataset. The company explained that the first 2 years of Kaplan–Meier data was most important because 75% of events occurred in this time. So, the tail of the curve was not informative because of very few observed events and a low number at risk. The company pointed out that its extrapolation closely matched the first 2 years of the Kaplan–Meier data whereas the EAG's data did not. The clinical experts agreed, noting that the EAG's extrapolation predicted a proportion of people still alive beyond 15 years. But this was implausible because no one lived past 16 years in the HMRN data. The committee asked the company how it determined the most appropriate extrapolation for survival. The company explained that it did

not inspect the hazards. Instead, it asked clinical experts to estimate survival at various timepoints. The log-normal distribution was chosen because it matched the experts' estimates more than other extrapolations. The company also added that it did not look at flexible models based on expert opinion because doing so risked overfitting the data because of a low number of events. The committee noted that it was unusual to apply the hazard ratios from the indirect comparison to the unadjusted epcoritamab data. It would prefer to see hazard ratios from the indirect comparison applied to comparator survival curves to generate the survival curves for epcoritamab. The committee concluded that the company's approach to modelling comparator survival was not robust. This is because verification seemed to be based mostly on the estimates matching expert-predicted survival. The committee considered that it would like to see stronger justifications for the approach selected, with an investigation into the underlying hazards and exploration of statistical fit. It also noted that its conclusion in section 3.5 to see alternative sources of comparator data used would need to be reflected in this additional analysis.

Utility values

Utility in PFS state for comparator

3.10 In the company's base case, utility values for the progression-free disease state were weighted according to the proportion of people reaching complete response on epcoritamab and other treatments at fourth line or later. The company noted that the clinical experts explained that people reaching complete response would be expected to have higher health-related quality of life, supporting this approach. The exact utility values used for each treatment arm are confidential and cannot be reported here. Clinical experts consulted by the EAG agreed that complete response is a determinant of health-related quality of life. But they also suggested that the impact of adverse events should be considered too, because people who reach complete response are likely to be on treatments for longer.

The EAG also considered that other factors such as duration of complete response should be included, otherwise the company approach is biased. So, the EAG base case used the same utility values for the progression-free disease states for epcoritamab and the comparator. This was taken from the EPCORE NHL-1 EQ-5D-3L data and not adjusted for complete response status. The committee considered that the utility values used by the company may be biased because they did not capture other factors linked to complete response that impact utility, including time in complete response and adverse events. The committee concluded that utility values used by the EAG that did not vary by complete response status were likely to be more appropriate for decision making.

Costs

Subsequent treatment costs

3.11 The company modelled subsequent treatment costs to be the same as the basket comparator included for treatment at fourth line or later. It explained that this approach was in line with clinical expert opinion. The EAG noted that clinical experts it consulted agreed that modelled subsequent treatments are appropriate. But, the EAG raised concerns that the clinical effects of subsequent treatments are modelled without associated costs in the company base case. This is because other treatments were included in EPCORE NHL-1, including systemic anti-lymphoma therapy, autologous stem cell transplant, and CAR-T therapy. The proportions of people having these treatments are confidential and cannot be reported here. The company explained that people who had CAR-T therapy are censored in the matching adjusted indirect comparison, so the costs should not be included. However, the EAG explained that although people who had CAR-T therapy were censored in the adjusted population, they were not censored in the unadjusted trial data that was used to model outcomes for treatment at fourth line or later in the company model. The EAG was unable to provide additional analysis to explore this uncertainty. But it suggested that a scenario

analysis that fully removed people who had CAR-T therapy, or included the associated CAR-T therapy costs, would help resolve some of the uncertainty. The committee concluded that it would like to see the analysis that was suggested by the EAG. That is, a scenario analyses that fully removed people who had CAR-T therapy from efficacy estimates, or included the associated costs for people who had CAR-T therapy in efficacy estimates.

Resource use costs

3.12 The company base case included once-monthly haematologist consultations for epcoritamab and it did not include positron emission tomography (PET) scans. It explained that the resource use estimates it included in its base case were verified by clinical experts. The EAG explained that clinical advice it received outlined that haematologist visits are weekly for the first month and then drop to monthly. The experts also suggested including 12-monthly PET scans. So, the EAG included weekly haematologist visits for the first month and monthly visits thereafter in its base case. It included 12-monthly PET scans in a scenario analysis. Submissions from the clinical experts for the committee meeting agreed that haematologist visits are weekly for the first month before reducing to monthly. The committee concluded that clinical opinion was clear that weekly haematologist visits for the first month and monthly visits thereafter are expected in clinical practice. So, it preferred to use these costs in cost-effectiveness modelling, as per the EAG's base case. It further concluded that it would consider both scenarios with and without 12-monthly PET scans in its decision making.

Adverse events costs

3.13 The company noted that limited adverse event data was available for chemotherapy (the most frequently used treatment in the comparator basket). Rituximab plus chemotherapy was the second most frequently used treatment in the comparator basket. So, adverse event incidence data for rituximab plus cyclophosphamide, doxorubicin, vincristine and

prednisone was used to generate costs for the entire comparator basket. This data was taken from NICE's technology appraisal guidance on axicabtagene ciloleucel for treating relapsed or refractory follicular lymphoma (TA894). The EAG asked the company to provide a scenario analysis also including costs based on adverse event data for lenalidomide plus rituximab and obinutuzumab plus bendamustine. This data was also available in TA894 as well as NICE's technology appraisal guidance on lenalidomide with rituximab for previously treated follicular lymphoma. The company used the adverse event rates for each treatment to represent the costs for the entire basket in separate scenarios. The EAG incorporated this analysis in its base case by weighting the adverse event rates for the relative use of each treatment, rather than using 1 treatment to represent the entire basket. The EAG also included grade 2 cytokine-release syndrome events that required treatment with tocilizumab in its base case. The committee concluded that the EAG approach to weighting adverse events was appropriate and should be used to model costs. It heard from clinical experts that clinical management of grade 2 cytokine-release syndrome events had changed and the occurrence was very low. So, it concluded it was not appropriate to include these adverse event costs in modelling.

Severity

3.14 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to quality-adjusted life years (QALYs; a severity modifier) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's manual on health technology evaluations. These were based on a mean age of 64.8 years and a proportion of females of 34.6%, based on EPCORE NHL-1 data. The estimated shortfalls met the criteria for a severity weight of 1.2 to be applied to the QALYs in the company base case. The EAG critiqued the company's estimates and decided they were

derived accurately for the company's base case. But corresponding shortfall estimates for the EAG's base case did not meet the criteria for a severity weight to be applied. So, a weight of 1 was applied to the QALYs in the EAG base case. The EAG explained this difference was mostly because of its preference for using HMRN data directly to model outcomes for treatment at fourth line or later (see section 3.9). The company identified that the EAG's base case was very close to meeting the criteria for a severity weight. It recalled the clinical expert opinion that the estimated survival for treatment at fourth line or later in the EAG's base case was too optimistic. It argued that had survival been modelled more accurately in the EAG base case, then the criteria for a severity weight would be met. During the committee meeting, the EAG acknowledged that its experts considered the true survival for treatment at fourth line or later to be in between the modelled survival in the EAG's and company's base cases. The committee understood that the estimated severity weight was very sensitive to modelling of survival for treatment at fourth line or later. It recalled its earlier requests for additional information to model comparator survival (see section 3.9). It also recalled the view of clinical experts and the company that the EPCORE NHL-1 population was at higher risk of death than the real-world population (see section 3.7). So, the committee was unable to conclude whether applying a severity weight greater than 1 to the QALYs was appropriate. This was because it needed the additional information it requested to consider the accuracy of modelled comparator survival. It also concluded that it would like to see severity calculations using baseline characteristics generalisable to the population who would have epcoritamab in the NHS if it were available.

Cost-effectiveness estimates

Acceptable ICER

3.15 NICE's manual on health technology evaluations 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. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty for which it requested further analyses (see section 3.16). It noted the level of uncertainty could change once additional information that it requested is shared. The committee concluded that it could not determine an acceptable ICER, but because of uncertainty it was towards the lower end of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). The committee noted it would reconsider this once further analyses have been provided.

Cost-effectiveness estimates and further analyses

3.16 The cost-effectiveness results included confidential prices for comparator treatments, so the exact results cannot be reported here. The company's deterministic base-case ICER was towards the lower end of the range normally considered a cost-effective use of NHS resources. But, the EAG's corresponding base-case ICER was considerably above the range normally considered cost effective. The committee concluded that it was unable to determine a committee-preferred base-case ICER, or determine an acceptable ICER. This is because of additional information it would like to see from the company to address uncertainties in the clinical and economic evidence. Specifically, the committee requested:

- an updated analysis that includes the full marketing authorisation population (including people having third-line treatment, see section 3.3)
- full justification, including a full breakdown of available evidence, and clear definition of the treatment at fourth line or later population if the full marketing authorisation population cannot be modelled (see section 3.3)

- longer follow-up data for the EPCORE NHL-1 dose-optimisation cohort (see section 3.4)
- a full exploration of alternative comparator data, an updated indirect treatment comparison, and an assessment of generalisability to the UK (see section 3.5 and section 3.7), as well as:
  - using alternative comparator data to validate model outcomes
  - using a simulated treatment comparison to validate the matching adjusted indirect treatment comparison, if possible
  - a full exploration of prognostic factors, especially for people with refractory disease
- more complex methods to adjust for COVID-19 deaths in EPCORE NHL-1 data instead of only censoring them, such as using causal inference (see section 3.6)
- stronger justifications for the company approach to modelling comparator survival, with an investigation into the underlying hazards and exploration of statistical fit (see section 3.9)
- scenario analyses that fully removes people who had CAR-T therapy from efficacy estimates, or includes the associated costs for people who had CAR-T therapy in efficacy estimates (see section 3.11).

The committee concluded that it could not recommend epcoritamab for routine use. It was unable to determine the most plausible ICER because of uncertainty in the clinical and economic evidence.

Other factors

Equality

3.17 The committee did not identify any equality issues.

Conclusion

Recommendation

3.18 The committee recalled the significant unmet need for treatment options for relapsed or refractory follicular lymphoma. It also recalled the

uncertainties with the clinical and economic evidence and the additional information it had requested from the company, especially around exploring the possibility of modelling people having third line treatment. It noted that this meant it could not determine the most plausible ICER, or an acceptable ICER. So, the committee did not recommend epcoritamab for treating relapsed or refractory follicular lymphoma, either for routine NHS use.

4 Evaluation committee members and NICE project team

Evaluation committee members

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

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Richard Nicholas

Vice chair, technology appraisal committee C

NICE project team

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

Owen Swales

Technical lead

Michelle Green

Technical adviser

Leena Issa

Project manager

Adam Brooke

Principal technical adviser

ISBN: [to be added at publication]