SMC2632

epcoritamab concentrate for solution for injection and solution for injection (Tepkinly®)

AbbVie Ltd

10 May 2024

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

ADVICE: following a full submission assessed under the end of life and orphan equivalent medicine process

epcoritamab (Tepkinly®) is accepted for use within NHSScotland.

Indication under review: as monotherapy for the treatment of adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

In a phase I/II open-label study, 62% of patients treated with epcoritamab who had R/R DLBCL after two or more lines of systemic therapy achieved objective response.

This advice applies only in the context of approved NHSScotland Patient Access Scheme (PAS) arrangements delivering the cost-effectiveness results upon which the decision was based, or PAS/ list prices that are equivalent or lower.

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

Vice Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Epcoritamab is a bispecific antibody that binds to a specific extracellular epitope of CD20 on B cells and to CD3 on T cells. The activity of epcoritamab is dependent on simultaneous engagement of CD20-expressing cancer cells and CD3-expressing endogenous T cells, which induces specific T-cell activation and T-cell-mediated killing of CD20-expressing cells.[1]

Epcoritamab is administered by subcutaneous injection in 28-day cycles and should be administered until disease progression or unacceptable toxicity. Dosing begins with a step-up dosing schedule leading to the recommended full dose of 48 mg, administered weekly (cycles 1 to 3); every two weeks (cycles 4 to 9) and every four weeks (from cycle 10 onwards). For full information on administration of epcoritamab, including recommended pre-medication / prophylaxis treatment and epcoritamab dose step-up schedule, refer to Summary of Product Characteristics (SPC).[1]

1.2. Disease background

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma (NHL), accounting for approximately 30% to 40% of all cases. The incidence increases with age with a median age at diagnosis of 64 years. Risk factors include a family history of lymphoma, autoimmune disease, human immunodeficiency virus (HIV) infection, hepatitis C virus (HCV) seropositivity, a high body mass as a young adult and some occupational exposures. Although approximately half of newly diagnosed patients with DLBCL receive curative treatment, the disease is aggressive and approximately 30% of cases relapse and 10% to 15% are refractory to first-line therapy.[2, 3, 4]

1.3. Treatment pathway and relevant comparators

Primary treatment of relapsed/refractory DLBCL depends on the individual's eligibility for transplant. Enrolment in clinical trials is usually considered where possible. Guidelines recommend that patients deemed fit for transplant receive salvage chemotherapy followed by autologous stem cell transplant (ASCT). For patients with relapsed or refractory DLBCL after two or more lines of systemic therapy, the CAR-T cell products axicabtagene ciloleucel and tisagenlecleucel should be considered; SMC has accepted axicabtagene ciloleucel (SMC2189) and tisagenlecleucel (SMC2200) in this setting. For patients who are not candidates for haematopoietic stem cell transplant (HSCT), polatuzumab vedotin in combination with bendamustine and rituximab is a treatment option (SMC2524). Gemcitabine or etoposide-based chemotherapy regimens may also be used in this setting in combination with rituximab. Tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy for the treatment of adult patients with relapsed or refractory DLBCL who are not eligible for ASCT is not recommended by SMC (SMC2522). SMC has also recently accepted polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP), for restricted use for patients with previously untreated DLBCL. Therefore, the treatment pathway for relapsed or refractory DLBCL is changing and availability of polatuzumab vedotin first line may displace its use in later lines of therapy.[2]

1.4. Category for decision-making process

Eligibility for interim acceptance decision option

Epcoritamab has conditional marketing authorisation from the Medicines and Healthcare Products Regulatory Agency.

Epcoritamab received an Innovation Passport allowing entry into the Innovative Licensing and Access Pathway.

Eligibility for a PACE meeting

Epcoritamab meets SMC end of life criteria and orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of epcoritamab for this indication comes from the EPCORE NHL-1 study. Data from the aggressive NHL (aNHL) cohort from the expansion part of the study were presented in the submission, details of which are presented in Table 2.1.

Table 2.1. Overview of relevant study[2, 5, 6]

Criteria	EPCORE NHL-1
Study design	Open-label, single-arm, multicentre, phase I/II study. Details below relate only to the aNHL cohort from the dose expansion part of the study.
Eligible patients	• Age ≥18 years • ECOG performance status of 0 to 2 • Documented CD20+ mature B-cell neoplasm according to WHO 2008 or 2016 classification: ○ DLBCL (de novo or transformed from all indolent subtypes including Richter's transformation), including patients with "double-hit" or "triple-hit" DLBCL (technically classified in WHO 2016 as HGBCL, with *MYC* and *BCL2* and/or *BCL6* translocations). Note: Other double-/triple-hit lymphomas were not eligible. • Relapsed or refractory disease, previously treated with at least two lines of systemic antineoplastic therapy including at least one anti-CD20 monoclonal antibody containing therapy.[a] • Either failed prior autologous HSCT or ineligible for autologous HSCT • Measurable disease
Treatments	Epcoritamab was administered by subcutaneous injection in 28-day cycles. In cycle 1, step-up dosing consisted of a 0.16 mg dose on day 1, followed by a 0.8 mg dose on day 8 and subsequent 48 mg doses on day 15 and thereafter until disease progression or unacceptable toxicity. Epcoritamab was administered once weekly during cycles 1 to 3, every two weeks during cycles 4 to 9 and every four weeks from cycle 10. Patients received premedication for CRS 30 to 120 minutes before the first four doses of epcoritamab (optional for subsequent doses).
Primary outcome	ORR (IRC-assessed, using Lugano criteria).
Secondary outcomes	DOR, DOCR, PFS, OS.
Statistical analysis	No formal statistical hypotheses were formulated.

[a] relapsed disease was defined as recurrence at least 6 months after completion of therapy; refractory disease was defined as progression either during therapy or within 6 months of completion of therapy.

Abbreviations: aNHL = aggressive non-Hodgkin lymphoma; CRS = cytokine release syndrome; CT = computed tomography; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; FDG-PET = fluorodeoxyglucose (FDG)-positron emission tomography (PET); FL3B = follicular lymphoma grade 3B; HGBL = high-grade B-cell lymphoma; HSCT = hematopoietic stem cell transplantation; IRC = independent review committee; IV = intravenous; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PMBCL = primary mediastinal (thymic) large B-cell lymphoma; WHO = World Health Organisation.

At the primary analysis of the aNHL expansion cohort (data cutoff 31 January 2022), the median follow-up was 10.7 months. The overall response rate (ORR) was 62% in patients with DLBCL, with 39% of patients in complete response. The company provided data at a later cutoff (21 April 2023) which are confidential. [7]

Details are presented in Table 2.2 below.

Table 2.2. Key efficacy results from the DLBCL group in the aNHL expansion cohort of EPCORE NHL-1.[1, 2, 8]

	Epcoritamab (n=139)	
	Primary analysis (Data cutoff 31 January 2022)	**Updated analysis (Data cutoff 30 June 2022)**
Primary outcome: ORR (IRC-assessed, Lugano criteria)		
ORR (CR+PR), %	62%	62%
CR, %	39%	39%
PR, %	23%	23%
SD, %	2.9%	*
Secondary outcome: DOR (IRC-assessed, Lugano criteria)		
Median DOR, months	12.0	15.6
Secondary outcome: OS		
Events	56	*
Median OS, months	NR	18.5
OS rate at 12 months	56%	*
Secondary outcome: PFS (IRC-assessed, Lugano criteria)		
Events	90	*
Median PFS, months	4.4	4.4
PFS rate at 12 months	37%	*

Abbreviations: CI = confidence interval; CR = complete response; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; IRC = independent review committee; KM = Kaplan-Meier; NA = not available; NR = not reached; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; SD = stable disease.

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

2.2. Health-related quality of life outcomes

Health-related quality of life (HRQoL) was assessed using the Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) questionnaire and EQ-5D-3L. These instruments were used on day 1 of cycles 1, 3, 5, 7 and 9 and at the end of treatment visit. In addition, six questions from the FACT-Lym (body pain, fever, night sweats, lack of energy, tires easily, weight loss) were assessed

on day 1 of cycles 2, 4, 6, 8 and 10 and then every cycle until end of treatment. Overall, consistent improvements were observed across all six questions from the FACT-Lym questionnaire from cycles 2 to 13, with improvements that exceeded the minimally important differences in the lymphoma subscale (FACT-LymS) and the EQ-5D-3L visual analogue scale (VAS).[2, 9]

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence versus relevant comparators, unanchored matching adjusted indirect comparisons (MAICs) were performed to generate comparative efficacy estimates for the economic analyses. Details are presented in Table 2.3.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Unanchored MAICs.
Population	Adult patients with relapsed or refractory LBCL.
Comparators	Rituximab-based chemoimmunotherapy, axicabtagene ciloleucel, tisagenlecleucel (scenario analysis only), polatuzumab vedotin plus BR.
Studies included	EPCORE NHL-1 (data for epcoritamab), SCHOLAR-1 (data for rituximab-based chemoimmunotherapy), ZUMA-1 (data for axicabtagene ciloleucel), JULIET (data for tisagenlecleucel, in scenario analysis only), GO29365 (data for polatuzumab vedotin plus BR), Northend et al., 2022 (RWE data for polatuzumab vedotin plus BR).
Outcomes	OS, PFS (for all comparators except rituximab-based chemoimmunotherapy), ORR, complete response rate.
Results	Epcoritamab had superior efficacy to rituximab-based chemoimmunotherapy in both the adjusted and unadjusted analyses. There was no significant difference in efficacy between epcoritamab and axicabtagene ciloleucel. For polatuzumab vedotin plus BR, there was also no significant difference in efficacy.

Abbreviations: BR = bendamustine and rituximab; CI = confidence interval; CR = complete response; HR = hazard ratio; LBCL = large B-cell lymphoma; MAIC = matching adjusted indirect comparison; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RWE = real-world evidence.

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

3. Summary of Safety Evidence

No comparative safety data are available. Refer to the SPC for more details.[1]

A pooled safety analysis was conducted which combined data from patients who received the full 48 mg dose from the dose escalation and dose expansion parts of EPCORE NHL-1, including 148 patients with DLBCL. At the time of the primary analysis (data cutoff 31 January 2022), the median duration of treatment was 3.9 months. Nearly all patients reported a treatment-emergent adverse event (AE) (99%), and these were considered treatment related in 84%. In the pooled DLBCL group (n=148), patients reporting a grade 3 and higher AE was 64% (related in 28%), patients with a reported serious AE were 59% (related in 36%), patients with an AE leading to dose delay were 34% and patients discontinuing treatment due to an AE was 8.1%.[2]

At the time of the primary analysis (data cutoff 31 January 2022), the most frequently reported treatment-related AEs of any grade with an incidence >10% in the pooled DLBCL group (n=148) were cytokine release syndrome (CRS) (49%), injection site reaction (24%), neutropenia (19%), fatigue (16%) and pyrexia (10%).[2]

The safety profile of epcoritamab is in line with what can be expected for a medicine of this class due to activation of T-cells, most notably an increased risk of CRS, immune effector cell-associated neurotoxicity syndrome (ICANS) and infections. Overall, regulators considered that the safety profile was acceptable with monitoring and management guidelines, given the advanced nature of the disease and the pretreated patient population under review.[1, 2]

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

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Promising, clinically relevant response rates and duration of response were demonstrated with epcoritamab in patients with relapsed or refractory DLBCL after two or more lines of systemic therapy. The complete response rate obtained with epcoritamab was considered particularly relevant by the regulators (39% in the DLBCL group in the aNHL expansion cohort at the time of the primary analysis).[2]
- Although patient numbers were small, epcoritamab appeared to have activity in patients who had prior CAR T-cell therapy (n=61, 44% of the relevant study population) with an ORR of 54% among the LBCL group in the aNHL cohort.[2]
- Epcoritamab is a subcutaneous treatment which may be advantageous for patients and the service compared with other treatments.

4.2. Key uncertainties

- EPCORE NHL-1 was a single-arm, phase I/II study which are prone to various biases. The treatment effect of epcoritamab relative to relevant comparators in clinical practice is therefore uncertain.
- Follow-up was of limited duration. For example, at the published latest data-cut (30 June 2022), median study duration follow-up was 15.7 months.[2] However, the company provided confidential data from a later data cut which provided reassurance.
- Sample size (n=139) was limited, however this may be expected for an orphan equivalent condition in a heavily pre-treated population.[2]
- CR and ORR are appropriate outcomes in phase II studies that measure anti-tumour activity. However, it may be unclear to what degree this anti-tumour activity corresponds to more robust measures of clinical benefit, such as overall survival (OS) or progression-free survival (PFS). Given the limitations above, it is difficult to interpret the clinically relevant outcomes PFS and OS.[2, 10]
- There may be generalisability issues with the study population in terms of prior treatments. Due to the evolving treatment pathway, patients in clinical practice may have received different prior treatments compared with the study population. The efficacy of epcoritamab following treatment with polatuzumab vedotin in combination with bendamustine plus rituximab is unknown.[2]

- There is no direct evidence comparing epcoritamab with relevant comparators in NHSScotland. The indirect comparisons presented by the submitting company have several limitations. Unanchored MAICs are inherently at risk of bias. There was no common control arm to anchor the indirect comparisons. Therefore, residual confounding due to unobserved characteristics and other characteristics that were not or could not be adjusted for may bias the results. Effective sample sizes were reduced considerably after matching, reflecting the poor overlap between study populations. Confidence intervals were wide suggesting uncertainty in the results. Safety and HRQoL were not assessed. In summary, due to these limitations, the MAIC results are highly uncertain.

4.3. GB/EMA conditional marketing authorisation specific obligations

As part of the specific obligations outlined by the European Medicines Agency (EMA), the submitting company should submit the final CSR for the key EPCORE NHL-1 study by Q3 2026.[2] In addition the submitting company should submit results by Q4 2024 for the ongoing, phase III EPCORE DLBCL-1 study, which compares epcoritamab with standard of care immunochemotherapy, in patients with DLBCL and HGBL at ≥ 1 line of prior systemic treatment .[2]

The EMA specific obligations are unlikely to address the key uncertainties in the clinical evidence presented.

4.4. Clinical expert input

Clinical experts consulted by SMC considered that epcoritamab fills an unmet need in this therapeutic area, as there are limited satisfactory treatment options currently available. Clinical experts considered epcoritamab to be a therapeutic advancement as an additional treatment option that can achieve disease control in some patients. They stated that epcoritamab would be used an alternative to CAR-T cell treatments, or in patients where CAR-T cell treatment is inappropriate (for example if a patient was not considered fit enough for CAR-T cell treatment), or in patients who have received CAR-T cell treatment and have experienced disease progression.

4.5 Service implications

Epcoritamab may be less burdensome to the service than CAR-T cell treatments and is immediately available (there are lead times associated with making CAR-T cell treatments). However, when compared with other treatment options, it may be associated with increased service burden. Patients need to be hospitalised to administer the first full dose of epcoritamab and will need careful monitoring for adverse events such as CRS and neurological adverse events. Epcoritamab is administered until disease progression or unacceptable toxicity which is less advantageous than a fixed duration treatment.

5. Summary of Patient and Carer Involvement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of epcoritamab, as an orphan-equivalent/end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Relapsed or refractory DLBCL is an aggressive type of lymphoma (blood cancer) associated with

poor prognosis and short life expectancy. Patients can experience a wide variety of symptoms, including enlarged lymph nodes, abdominal pain, nausea, cough, breathlessness, and B symptoms such as fevers, night sweats and unexplained weight loss. In addition to the physical symptoms of relapsed or refractory DLBCL, there is a significant mental burden for patients caused by worrying about relapsing or not responding to treatment; this can lead to anxiety or insomnia in some.

- There are a limited number of treatment options at present for relapsed or refractory DLBCL, and these treatments have limited efficacy and considerable side effects. Treatment regimens that include chemotherapy can have challenging and persistent side effects and CAR-T cell therapies are only provided by two hospitals in Scotland, and some patients may experience disease progression whilst they wait for the treatment to be manufactured. There are fewer treatment options for patients who have already received CAR-T therapy or polatuzumab vedotin (at earlier lines of treatment). There is therefore a high unmet need for patients with relapsed or refractory DLBCL.

- Epcoritamab has the potential to benefit patients greatly in this setting. It is believed to be a well-tolerated treatment which may achieve durable disease control in patients, that could result in improvements in survival and help to maintain a high quality of life. Some patients may spend less time in hospital compared with other treatments. The availability of epcoritamab as a treatment option when disease relapses or fails to respond to treatment will likely have a large impact on the mental wellbeing of patients It also provides an immediately and widely available treatment option with a convenient subcutaneous route of administration, which could be particularly beneficial for patients who do not live near to the two specialist CAR-T treatment centres in Scotland. Treatment with epcoritamab is until disease progression or unacceptable toxicity; however, the increased access to medical support associated with continuous therapy may be beneficial for some.

- Friends, family, and carers experience significant stress and anxiety worrying about relapses or lack of treatment response, and often have to take on financial, caring, and at-home responsibilities. The availability of epcoritamab is expected to alleviate some of the anxiety experienced by family members and carers, and if patients respond to treatment, the burden of care may be reduced as patients enjoy more independence.

- PACE participants noted that careful monitoring for CRS adverse events is required with epcoritamab. However, these adverse events are mainly mild in severity, easily managed, and ultimately would not deter patients from wanting to commence treatment on epcoritamab, since it is a promising treatment that can potentially prevent or prolong disease progression.

Additional Patient and Carer Involvement

We received patient group submissions from Lymphoma Action and Blood Cancer UK, which are both registered charities. Lymphoma Action has received 6.7% pharmaceutical company funding in the past two years, including from the submitting company. Blood Cancer UK has received 5.41% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Blood Cancer UK participated in the PACE meeting. The key points of the

submissions from both patient groups have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime time horizon, defined as 45 years.
Population	Adult patients with R/R DLBCL after two or more lines of systemic therapies. Economic results were presented for two separate populations as follows: • **Population A:** patients who are ineligible for, or choose not to receive, intensive therapies; and • **Population B:** patients who are eligible to receive intensive therapies.
Comparators	**Population A** The comparator is rituximab-based chemoimmunotherapy (R-based CIT). The company used rituximab in combination with gemcitabine and oxaliplatin (R-GemOx) as a proxy for all R-based CITs based on feedback from clinical and economic experts they contacted. **Population B** The company noted that axicabtagene ciloleucel and tisagenlecleucel are accepted for use by the SMC; however, they state that axicabtagene ciloleucel is more widely used in Scottish clinical practice as a result of its higher efficacy. Therefore, in terms of the economic evaluation, they considered axicabtagene ciloleucel a suitable proxy for analyses comparing epcoritamab versus CAR-T therapies. **Note:** results versus tisagenlecleucel are provided as scenario analyses in Table 6.3.
Model description	A *de novo* economic model was developed in Microsoft Excel®. The type of model used was a partitioned survival analysis model which included three health states: PFS, post-progression survival and death.
Clinical data	The key sources of clinical evidence used in the economic evaluation are the EPCORE™ NHL-1 study[5,9] for epcoritamab and unanchored MAICs conducted by the company. MAICs were required to generate comparative efficacy evidence for the economic analyses due to EPCORE™ NHL-1 being a single-arm study.
Extrapolation	The company used what are considered 'standard' methods for extrapolation of clinical data and selected particular models for extrapolation in their base case analyses using a combination of goodness-of-fit statistics, visual inspection and clinical expert feedback. The specific distributions used by the company to extrapolate PFS, time-to-discontinuation (TTD), and OS outcomes for epcoritamab and R-based CIT in their base case analysis are shown in the table below. The company comment that PFS and TTD data were not available from the SCHOLAR-1 study, thus PFS and TTD were extrapolated for R-based CIT using the HR for OS derived from the MAIC. No explicit long-term remission assumptions were included.

<table>
<tr><td></td><td>
<table>
<tr><th colspan="3">Population A</th></tr>
<tr><th>Outcome</th><th>Epcoritamab</th><th>R-based CIT</th></tr>
<tr><td>PFS</td><td>Generalised gamma</td><td rowspan="2">HR for OS from MAIC applied (PFS and TTD not reported in SCHOLAR-1)</td></tr>
<tr><td>TTD</td><td>Exponential</td></tr>
<tr><td>OS</td><td>Lognormal</td><td>Lognormal</td></tr>
</table>
The specific distributions used by the company to extrapolate PFS, TTD, and OS outcomes for epcoritamab and axicabtagene ciloleucel in their base case analysis are shown in the table below.
<table>
<tr><th colspan="3">Population B</th></tr>
<tr><th>Outcome</th><th>Epcoritamab</th><th>Axicabtagene Ciloleucel</th></tr>
<tr><td>PFS</td><td>Gompertz</td><td>Gompertz</td></tr>
<tr><td>TTD</td><td>Exponential</td><td>Not applicable</td></tr>
<tr><td>OS</td><td>Gompertz</td><td>Gompertz</td></tr>
</table>
</td></tr>
<tr><td>Quality of life</td><td>Health benefits were quantified in quality-adjusted life-years (QALYs). The health effects accounted for in determining these included: changes in health state (eg transitioning from a progression-free form of disease to progressed disease), age-related effects reported in the literature, and the impact of adverse events associated with treatment.

Health status was measured using the EQ-5D-3L questionnaire and subsequently converted into preference-based single indices using a UK time trade-off algorithm.</td></tr>
<tr><td>Costs and resource use</td><td>Medicine-related costs included in the analysis for the intervention and comparators were as follows: medicine acquisition, administration, monitoring, subsequent treatment (including administration and monitoring), and adverse events.

Other healthcare resource use included in the analysis constituted resources associated with ongoing monitoring for patients (eg general practitioner and nurse appointments, radiographic imaging, outpatient appointments with consultants, laboratory based tests, etc) and end of life care.</td></tr>
<tr><td>PAS</td><td>A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

PAS discounts are in place for axicabtagene ciloleucel and tisagenlecleucel. Discounts associated with these therapies were included in the results used for decision-making by using estimates of their PAS prices.</td></tr>
</table>

Abbreviations: PFS = progression-free survival; OS = overall survival; TTD = time-to-discontinuation; PAS = patient access scheme; PASAG = patient access scheme assessment group; HRQoL: health-related quality-of-life

6.2. Results

The main economic results for Population A and Population B are presented at list prices for all treatments in Table 6.2.

Population A

Disaggregated results indicate that the higher QALYs associated with epcoritamab compared to R-based CIT are due to a combination of increased life expectancy and a longer amount of time living progression-free. The higher costs associated with epcoritamab stem from a combination of its

acquisition cost and increased disease management healthcare resource use due to longer life expectancy.

Population B

Disaggregated results indicate that the higher QALYs associated with epcoritamab compared to axicabtagene ciloleucel are due to a combination of increased life expectancy and a longer amount of time living progression-free. Cost savings associated with epcoritamab stem from its lower combined acquisition, monitoring, and administration costs.

Table 6.2: Base case results at list prices

Technologies	ICER (£/QALY)
Population A: Epcoritamab versus R-base CIT	49,594
Population B: Epcoritamab versus axicabtagene ciloluecel	Dominant

Abbreviations: CIT: chemoimmunotherapy; ICER: incremental cost-effectiveness ratio; R: rituximab; QALYs: quality-adjusted life years; Dominant= The assessed medicine was estimated as having lower costs and greater health outcomes than the comparator

6.3. Sensitivity analyses

The submitting company conducted a range of different types of sensitivity analyses which highlighted areas of uncertainty regarding economic results, with other scenarios specified by the assessment team. A selection of these results, at list prices for all treatments, are included in Table 6.3. Additional scenarios include tisagenlecleucel as a comparator in Population B, Table 6.4.

Table 6.3: Key scenario analyses at list prices

Scenario	Parameter	Base case	Scenario	ICER (£/QALY)
Population A: Patients ineligible for, or chose not to receive, intensive therapies (comparator = R-based CIT)				
0	**Base case**			49,594
1	PFS extrapolation **(epcoritamab)**	Generalised gamma	Lognormal	61,545
2			Weibull	65,664
3	TTD extrapolation **(epcoritamab)**	Exponential	Weibull	55,091
4	OS extrapolation **(epcoritamab)**	Lognormal	Weibull	64,697
5	OS extrapolation **(R-based CIT only)**	Lognormal	Generalised gamma	51,844
6	Data source for health state utility values	Derived from EPCORE™ NHL-1	Derived from ZUMA-1	53,224
7	Time horizon	45 years	10 years	74,277
8			20 years	55,555
9	Scenarios 2 + 3 + 4 combined			87,562
10	Extrapolation approach	As described in Table 6.1	Piecewise KM approach where KM data are used directly until 24 months. Long-term remission assumption applied to all patients progression-free after 36 months.	35,751
Population B: Patients who are eligible to receive intensive therapies (comparator = axicabtagene ciloleucel)				
0	**Base case**			Dominant
1	PFS extrapolation **(epcoritamab)**	Gompertz	Log-logistic	Dominant
2			Lognormal	Dominant
3			Weibull	Dominant
4	TTD extrapolation **(epcoritamab)**	Exponential	Lognormal	Dominant
5	OS extrapolation **(epcoritamab)**	Gompertz	Log-logistic	SW quadrant (142,646)
6			Lognormal	SW quadrant (148,688)
7			Weibull	SW quadrant (85,048)
8	Data source for health state utility values	Derived from EPCORE™ NHL-1	Derived from ZUMA-1	Dominant

Scenario	Parameter	Base case	Scenario	ICER (£/QALY)
Population A: Patients ineligible for, or chose not to receive, intensive therapies (comparator = R-based CIT)				
9	Time horizon	Time horizon	10 years	Dominant
10			20 years	Dominant
11	Scenarios 3 + 4 + 7 combined			SW quadrant (56,520)
12	Extrapolation approach	As described in Table 6.1	Piecewise KM approach where KM data are used directly until 24 months. Long-term remission assumption applied to all patients progression-free after 36 months.	Dominant

Abbreviations: PFS: progression-free survival; TTD: time-to-discontinuation; OS: overall survival; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio

Table 6.4: Key scenario analyses at list prices

Scenario	Parameter	Base case	Scenario	ICER (£/QALY)
Population B: Patients who are eligible to receive intensive therapies (comparator = tisagenlecleucel)				
0	**Base case**			Dominant
1	PFS extrapolation **(epcoritamab)**	Gompertz	Log-logistic	Dominant
2	TTD extrapolation **(epcoritamab)**	Exponential	Weibull	Dominant
3	OS extrapolation **(epcoritamab)**	Generalised gamma	Log-logistic	SW quadrant (263,063)
4	Data source for health state utility values	Derived from EPCORE™ NHL-1	Derived from ZUMA-1	Dominant
5	Time horizon	45 years	10 years	Dominant
6			20 years	Dominant
7	Scenarios 1 + 2 + 3 combined			SW quadrant (165,166)
8	Extrapolation approach	As described in Table 6.1	Piecewise KM approach where KM data are used directly until 24 months. Long-term remission assumption applied to all patients progression-free after 36 months.	Dominant

Abbreviations: PFS: progression-free survival; TTD: time-to-discontinuation; OS: overall survival; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio

6.4. Key strengths

- HRQoL data collected during the EPCORE NHL-1 study using the EQ-5D-3L questionnaire (the preferred method for SMC submissions) were available to inform the health state utility value estimates for patients in the PFS and 'post-progression' health states of the economic model.
- A comprehensive range of different types of healthcare resource use (medications and non-medication related) appears to be included in the economic evaluation. Furthermore, data sources used to value healthcare resource use are consistent with SMC guidance on economic submissions.
- A range of different types of sensitivity analyses were conducted by the company facilitating insight into the relative contribution of parametric and structural uncertainty on economic results.

6.5. Key uncertainties

- Several limitations were noted with the study methodology in EPCORE NHL-1 such as its single-arm, open-label study design which may have biased the assessment of efficacy, particularly time-to-event outcomes, such as OS and PFS, as well as HRQoL (although PFS was assessed by blinded independent central review, which reduces the risk of bias). This raises concerns regarding the reliability of the data available to extrapolate health outcomes for epcoritamab to the time horizon used in the economic evaluation.
- Long-term efficacy and safety data from EPCORE NHL-1 remain limited therefore health outcomes in the economic evaluation require a significant degree of extrapolation (model time horizon: 45 years). Furthermore, it is uncertain how many patients will achieve long-term disease control with epcoritamab, yet the models used to extrapolate health outcomes in the company's base case implicitly assume this is a likely outcome for a significant number of patients. Use of alternative methods for extrapolating OS have a particularly large impact in population B as shown in table 6.3. and 6.4. Following the New Drugs Committee meeting, the company also provided analysis using alternative approaches to the extrapolation used in the base case. These used piecewise approaches to extrapolation and incorporated a long term remission assumption for patients who remain progression-free at 36 months.
- There is no direct evidence comparing epcoritamab with relevant comparators in NHSScotland. The company therefore conducted a series of unanchored MAICs to generate relative efficacy data versus these comparators. The use of unanchored MAICs to generate such data significantly increases the uncertainty associated with economic results relative to direct evidence comparing intervention and comparators.
- SMC clinical experts highlighted polatuzumab vedotin plus BR as a relevant comparator, but the company did not account for this in their economic evaluation, citing recent SMC guidance on polatuzumab vedotin that might limit its use in this indication. While recent guidance from SMC suggests that use of polatuzumab vedotin in this indication may decrease over time, SMC clinical expert responses imply that it is still a commonly used treatment. Following the New Drugs Committee meeting, the company did however provide an additional comparison versus this comparator, which at prices including all PAS, was confidential.

7. Conclusion

The Committee considered the benefits of epcortimab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as epcortimab is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted epcortimab for use in NHSScotland.

8. Guidelines and Protocols

The British Committee for Standards in Haematology published guidelines for the management of DLBCL in 2016.[4] This guidance predates the availability of epcoritamab; therefore, no specific recommendations were made for this medicine.

The National Institute for Health and Care Excellence (NICE) published clinical guideline NG52: Non-Hodgkin's lymphoma: diagnosis and management in July 2016, which was last updated in October 2021.[12]

The European Society for Medical Oncology (ESMO) published DLBCL: ESMO clinical practice guidelines for diagnosis, treatment and follow-up in 2002. This guidance was subsequently updated in 2012 and again in 2015.[3] This guideline predates the availability of epcoritamab; therefore no specific recommendations were made.

9. Additional Information

9.1. Product availability date

17 January 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per cycle (£)
epcoritamab	**0.16 mg priming dose on day 1, 0.8 mg intermediate dose on day 8 and 48 mg full dose on days 15 and 22 of cycle 1 and thereafter (weekly during cycles 2 to 3, every 2 weeks during cycles 4 to 9 and every 4 weeks during cycle 10 and beyond), until disease progression or unacceptable toxicity.**	**Cycle 1: £14,231** **Cycles 2 to 3 (per cycle): £26,272** **Cycles 4 to 9 (per cycle): £13,136** **Cycle 10 and beyond (per cycle): £6,568**

Costs from MIMS online on 02 February 2024. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 71 patients eligible for treatment with epcoritamab in year 1, rising to 358 patients in year 5, to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

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

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12. National Institute of Health and Care Excellence (NICE). Non-Hodgkin's lymphoma: diagnosis and management, NICE guideline NG52. https://www.nice.org.uk/. Last updated October 2021.

This assessment is based on data submitted by the applicant company up to and including **15 March 2024**.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

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

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

Advice context:

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

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.