SMC2628

axicabtagene ciloleucel dispersion for infusion (Yescarta®)

Kite, a Gilead company

09 February 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 medicine process

axicabtagene ciloleucel (Yescarta®) is not recommended for use within NHSScotland.

Indication under review: for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy.

In a randomised, open-label, phase III study, axicabtagene ciloleucel significantly improved event-free survival compared with standard of care in patients with large B-cell lymphoma.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC.

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

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Axicabtagene ciloleucel is an advanced therapy medicinal product, which provides CD19-directed genetically modified autologous T-cell immunotherapy. To prepare axicabtagene ciloleucel, the patient's T cells are harvested and genetically modified ex vivo to express the anti-CD19 chimeric antigen receptor (CAR). Anti-CD19 CAR-positive viable T cells are expanded and intravenously infused back into the patient, who has received lymphodepleting chemotherapy, where they can recognise and eliminate CD19 expressing target cells. A single dose of axicabtagene ciloleucel contains a target dose of 2 x 10^6 (range: 1 × 10^6 to 2 × 10^6 cells/kg) CAR-positive viable T cells per kg of body weight (or maximum of 2 x 10^8 CAR-positive viable T cells for patients 100kg and above). Further information on pre-treatment with lymphodepleting chemotherapy, administration of axicabtagene ciloleucel, and monitoring is included in the Summary of product characteristics (SPC).[1]

1.2. Disease background

Large B-cell lymphoma (LBCL) represents a subset of aggressive Non-Hodgkin's Lymphoma (NHL) originating from B cells, which includes the fast-growing DLBCL and HGBL. LBCL represents a predominant subtype of NHL, constituting 30% to 40% of cases, and DLBCL accounts for more than 80% of LBCL cases (while HGBL accounts for up to 13% of LBCL cases). Patients have varying symptoms, which may include painless lumps, fevers, and fatigue. The prognosis of patients with relapsed or refractory DLBCL or HGBL is extremely poor.[2-4]

1.3. Company proposed position

The submitting company has requested that axicabtagene ciloleucel is restricted for use in patients with primary refractory or early relapse (≤ 12 months of first-line therapy) DLBCL and HGBL who are intended for transplant.

1.4. Treatment pathway and relevant comparators

For patients who have primary refractory disease or disease that relapses after first-line chemo-immunotherapy, guidelines recommend second-line, salvage treatment with multi-agent immunochemotherapy (such as rituximab with cisplatin, cytarabine, dexamethasone [R-DHAP], rituximab with ifosfamide, carboplatin, etoposide [R-ICE], rituximab with cisplatin, gemcitabine, dexamethasone [R-GDP]). In chemosensitive patients (that is, if there has been at least a partial response to chemotherapy), high-dose chemotherapy with autologous stem cell transplantation (auto-SCT) as remission consolidation should be considered. Consolidation with allogeneic SCT can also be considered for patients with chemosensitive disease that relapses after, or in whom stem cell harvesting is not possible.[5-8]

1.5. Category for decision-making process

Eligibility for a PACE meeting

Axicabtagene ciloleucel meets SMC end of life and orphan 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 axicabtagene ciloleucel in the licensed indication comes from ZUMA-7. Details are summarised in Table 2.1.

Table 2.1. Overview of the relevant study

Criteria	ZUMA-7
Study design	Randomised, open-label, active-controlled, international, phase III study

Eligible patients	The key inclusion criteria were:
	• Histologically proven LBCL including the following types defined by the World Health Organization in 2016:
	  ○ DLBCL not otherwise specified (including ABC/GCB)
	  ○ HGBL with or without myelocytomatosis and B-cell lymphoma 2 apoptosis regulator and/or B-cell lymphoma 6 transcription repressor rearrangement
	  ○ DLBCL arising from follicular lymphoma
	  ○ T-cell/histiocyte rich LBCL
	  ○ DLBCL associated with chronic inflammation
	  ○ Primary cutaneous DLBCL, leg type
	  ○ Epstein-Barr virus-positive DLBCL
	• Relapsed or refractory disease after first-line chemoimmunotherapy.
	  ○ Relapsed disease defined as complete remission to first-line therapy followed by biopsy-proven disease relapse ≤ 12 months of therapy.
	  ○ Refractory disease defined as no complete remission to first-line therapy; patients who were intolerant to first-line therapy were excluded.
	• Received adequate first-line therapy including at a minimum:
	  ○ Anti-CD20 monoclonal antibody unless the investigator determined the tumour was CD20 negative, and
	  ○ An anthracycline-containing chemotherapy regimen
	• Intended to proceed to HDT-auto-SCT if there was a response to second-line therapy
	• Had radiographically documented disease
	• No known history or suspicion of central nervous system involvement by lymphoma
	• At least 2 weeks or 5 half-lives, whichever was shorter, had elapsed since any prior systemic cancer therapy at the time the patient provided consent
	• Age 18 years or older at the time of informed consent
	• Eastern Cooperative Oncology Group performance status of 0 or 1

Treatments	Axicabtagene ciloleucel was administered after a 3-day lymphodepleting chemotherapy regimen (consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day; followed by 2 rest days). A single infusion of axicabtagene ciloleucel was administered intravenously at a target dose of 2 x 10^6 anti-CD19 CAR-T cells/kg (minimum dose of 1 x 10^6 anti-CD19 CAR-T cells/kg; for patients weighing > 100 kg, the maximum flat dose was 2 x 10^8 anti-CD19 CAR-T cells). Bridging therapy with corticosteroids was allowed prior to lymphodepleting chemotherapy at the discretion of the investigator, but chemoimmunotherapy was not allowed as bridging therapy. Standard of care consisted of protocol-defined salvage chemotherapy regimens (R-ICE, R-DHAP/R-DHAX, R-ESHAP, or R-GDP) as selected by the treating investigator, administered every 2 to 3 weeks for 2 to 3 cycles. Responders were to proceed with HDT-auto-SCT per institutional or regional standards. Patients not responding to salvage chemotherapy could receive additional treatment off protocol.

Randomisation	Patients were randomised equally. Randomisation was stratified by response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (0 to 1 versus 2 to 3) at screening.
Primary outcome	EFS defined as the time from randomisation to the earliest date of disease progression according to the Lugano classification, the commencement of new therapy for lymphoma, death from any cause, or a best response of stable disease up to and including the response on the day 150 assessment after randomisation according to blinded central review.
Key secondary outcomes	• ORR defined as the incidence of either a complete response or a partial response by the Lugano Classification as determined by blinded central review. • OS defined as the time from randomisation to death from any cause.
Statistical analysis	A hierarchical statistical testing strategy was applied in the study for primary and key secondary efficacy outcomes (starting with EFS, followed by ORR, and ultimately OS) with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Efficacy analyses were performed in the intention-to-treat population, which included all patients who underwent randomisation.

Abbreviations: ABC = activated B-cell; Auto-SCT, Autologous stem cell transplant; CAR, Chimeric antigen receptor; DLBCL, Diffuse large B-cell lymphoma; EFS, Event-free survival; GCB = germinal centre B-cell; HDT, High-dose therapy; HGBL, high-grade B-cell lymphoma; LBCL, large B-cell lymphoma; ORR, Objective response rate; OS, Overall survival; R-ICE rituximab with ifosfamide, carboplatin, etoposide; R-DHAP rituximab with cisplatin, cytarabine, dexamethasone; R-DHAX rituximab with dexamethasone, cytarabine, and oxaliplatin; R-ESHAP rituximab with etoposide. methylprednisolone cytarabine, cisplatin; R-GDP rituximab with gemcitabine, dexamethasone, cisplatin. SCT = stem cell transplant.

Axicabtagene ciloleucel significantly improved event-free survival (EFS) when compared with standard of care (SoC). Details of the primary and key secondary outcomes are presented in Table 2.2.

Table 2.2. Primary and key secondary outcome results[4, 9-11]

	axicabtagene ciloleucel (n=180)	**SoC (n=179)**	**axicabtagene ciloleucel (n=180)**	**SoC (n=179)**
Data cut-off	**Primary EFS analysis - data cut-off 18 March 2021**		**primary OS analysis - data cut-off 25 January 2023**	
Primary outcome: EFS by blinded central review				
Median follow-up	24.9 months.		-	
Event	108	144		
Median EFS, months, (95 % CI)	8.3 (4.5 to 15.8)	2.0 (1.6 to 2.8)		
Hazard ratio (95 % CI)	0.40 (0.31 to 0.51)			
Stratified p-value	P<0.001			
2-year EFS, %	40%	16%		
Key secondary outcome: ORR by blinded central review				
Responses, n (%)	150 (83 %)	90 (50 %)	-	
Difference (95 % CI)	33 % (23 to 42)			
Odds ratio (95 % CI)	5.31 (3.08 to 8.90)			
Stratified p-value	<.001			
Key secondary outcome: OS				
Median follow-up, months	24.7[a]	24.4[a]	47.2	

Deaths	72	85[b]	82	95
Median OS, months (95 % CI)	NR (28.3 to NE)	25.7 (17.6 to NE)[b]	NR (28.6 to NE)	31.1 (17.1 to NE)
Hazard ratio (95 % CI)	0.71 (0.52 to 0.97)[b]		0.73 (0.54 to 0.98)	
p-value	NS		P=0.03	
2-year OS, %	61%	51%[b]	60 %	51 %
4-year OS, %	-		55 %	46 %

Abbreviations: CI, confidence interval; EFS, event-free survival; NE, not estimable; NR, not reached; NS, not significant; ORR, Objective response rate; OS, Overall survival; SoC, standard of care.

[a] median follow-up times for OS using the reverse Kaplan Meier method

[b] The OS data presented are from post-hoc analyses. These were updated after the EFS primary analysis data cut-off date as the company had obtained additional survival follow-up for patients discontinued from ZUMA-7 that was not initially available at the time of the EFS primary analysis but occurred before the data cut-off date.

2.2. Evidence to support the positioning proposed by the submitting company

The study population of ZUMA-7 represents the proposed positioning**.**

2.3. Health-related quality of life outcomes

Health Related Quality of Life (HRQoL) was assessed using the Euro-QoL, 5 Dimensions, 5 Levels (EQ-5D-5L) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30 (EORTC QLQ-C30).

Patients treated with axicabtagene ciloleucel experienced clinically meaningful improvements in HRQoL compared to those receiving SoC. For the EORTC QLQ-C30 Global Health Status, the axicabtagene ciloleucel group showed a greater mean change from baseline with an estimated difference versus SoC of 18.1 by day 100 and 9.8 by day 150. The mean score for patients in this group reached or surpassed baseline scores by day 100, in contrast to the SoC group, in which the mean reached this point by Month 9. Similarly, for EORTC QLQ-C30 Physical Functioning, the axicabtagene ciloleucel group demonstrated a clinically meaningful improvement in mean score with an estimated difference versus SoC of 13.1 by day 100, with the mean returning to or exceeding baseline scores by day 150, whereas the SoC group achieved this by Month 12. The EQ-5D-5L visual analogue scale (VAS) scores also favoured axicabtagene ciloleucel, with an estimated difference in mean change versus SoC of 13.7 by day 100 and 11.3 by day 150, with the mean returning to or surpassing of baseline scores by day 100, compared to Month 9 for the SoC group. [4]

3. Summary of Safety Evidence

There are no new major safety concerns in this new population. Overall, the treatment-emergent adverse events (TEAEs) and risks were considered similar to what has been described for other CAR-T cell therapies and for axicabtagene ciloleucel in other indications, and are manageable with the current risk minimisation measures. [4] Patients must be monitored daily for the first 10 days following infusion for signs and symptoms of potential cytokine release syndrome, neurologic events and other toxicities.[1]

In the ZUMA-7 study at data cut-off 25 January 2023 all patients reported TEAE. In the axicabtagene ciloleucel (N=170) and SoC (N=168) groups respectively, patients reporting a grade 3

or higher adverse event (AE) were 91% versus 83%, patients with a reported serious AE were 56% versus 46%. [10]

The most frequently reported TEAEs of a grade 3 or higher with an incidence >10% in were: neutropenia (69% versus 41% in the axicabtagene ciloleucel group versus the SoC group), hypotension (11% versus 3%), anaemia (30% versus 39%), leukopenia (29% versus 22%), thrombocytopenia (15% versus 57%), hypophosphatemia (18% versus 13%), febrile neutropenia (3.5% versus 27%), and encephalopathy (12% versus 0). [10]

Fatal AE considered treatment related by the investigators occurred in one patient treated with axicabtagene ciloleucel (hepatitis B virus reactivation) and in two patients in the SoC cohort (both events [cardiac arrest and acute respiratory distress syndrome] were considered by the investigators to be related to high-dose chemotherapy). [10]

4. Summary of Clinical Effectiveness Considerations

The key strengths and uncertainties of the clinical case are summarised below.

4.1. Key strengths

- Results from the ZUMA-7 trial suggest that axicabtagene ciloleucel exhibits superior efficacy as a second-line therapy in adult patients with refractory or relapsed DLBCL or HGBL within 12 months of first-line chemoimmunotherapy completion, when compared to SoC. This was supported by EFS, objective response rate, and overall survival (OS) data.
- Axicabtagene ciloleucel is the first CAR-T cell therapy licensed for second-line use in patients with DLBCL or HGBL.
- Clinically meaningful improvements were also observed in HRQoL outcomes for axicabtagene ciloleucel compared with SoC in ZUMA-7.

4.2. Key uncertainties

- The protocol did not allow use of salvage chemotherapy in axicabtagene ciloleucel arm; only glucocorticoids were allowed as bridging therapy. SMC clinical experts suggested that this may differ from Scottish practice, as some patients may receive salvage chemotherapy while awaiting axicabtagene ciloleucel manufacturing/delivery. This approach in ZUMA-7 might have reduced the number of patients for whom urgent treatment was indicated, potentially biasing results in favour of axicabtagene ciloleucel.
- A high number of patients in the SoC arm received subsequent off-protocol cellular immunotherapy (57%). It is unclear whether this observed proportion in ZUMA-7 is significantly different from what would be seen in Scottish practice.
- In addition, some patients (8%) in the axicabtagene ciloleucel arm have subsequently been treated with cellular immunotherapy. [10] The submitting company noted a few patients in the axicabtagene ciloleucel arm received axicabtagene ciloleucel re-treatment. However, axicabtagene ciloleucel is licensed for single use. ZUMA-7 does not provide evidence to support re-treatment with a CAR-T cell therapy in patients previously treated with axicabtagene ciloleucel; and it is unknown whether some patients in practice would actually be re-treated with a CAR-T cell therapy. It is also uncertain to what extent re-treatment had an impact on outcomes.

- Another limitation is that EFS events were imputed as the randomisation date (in case of the initiation of a new lymphoma therapy in the absence of any evaluable disease assessment). This imputation approach resulted in some more events in the SoC group compared to the axicabtagene ciloleucel group (10 in SoC and 2 in axicabtagene ciloleucel), and this may have been influenced by patient preferences (to change to a different treatment than the assigned SoC) in this open-label study and introduces bias in favour of axicabtagene ciloleucel. This bias may affect the EFS estimates, but regulators noted it does not impact OS and should not significantly affect EFS to a degree that questions the treatment's benefit. [4]

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

4.3. Clinical expert input

Clinical experts consulted by SMC considered that axicabtagene ciloleucel fills an unmet need in this therapeutic area due to limited treatment options and poor prognosis. They considered that it is a therapeutic advancement, with significantly improved outcomes, including overall survival, demonstrated in the ZUMA-7 study.

4.4. Service implications

Clinical experts consulted by SMC considered that the introduction of this medicine will have implications for both patients and service delivery. Administration must be carried out in a hospital with appropriate facilities, specialist staff, and critical care bed capacity for managing potential adverse events. Increased hospitalisation is expected as ten days hospitalisation after the infusion are likely to be needed, and the patient must remain close to the specialist treatment centre for four weeks after receiving treatment.

The extremely high upfront acquisition cost for this single-dose treatment is likely to have significant service implications and is associated with financial risk to the service if the long-term predicted clinical benefits do not materialise.

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 **axicabtagene ciloleucel**, as an **end of life and orphan** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- DLBCL and HGBL are aggressive lymphomas causing severe symptoms like pain and lethargy, with rapid progression leading to very poor prognosis in the relapse/refractory setting, and a heavy impact on patients' daily life and mental health. These also place a substantial burden on carers and families.
- There is a significant unmet need for new therapies that would improve outcomes, including survival and quality of life, with a better side effect profile and reduced burden for patients.
- Axicabtagene ciloleucel has the potential to help address this unmet need by offering an alternative treatment option that could improve outcomes, including survival, cure rate,

restoration of normal life expectancy and quality of life compared with existing standard of care with intensive second-line chemotherapy followed by autologous stem cell transplant.

- It also appears to be a gentler treatment with a more favourable side effect profile and quicker recovery compared with existing standard of care.
- The aggressive nature of the disease often prevents patients from reaching CAR T-cell therapy at third line and axicabtagene ciloleucel shift from third to second line use for relapsed/refractory patients will provide an earlier chance at a potentially curative treatment.

Additional Patient and Carer Involvement

We received patient group submissions from: Anthony Nolan, Blood Cancer UK and Lymphoma Action. All three organisations are registered charities. Anthony Nolan has received 6% 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. Lymphoma Action has received 6.7% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from all three of the patient groups participated in the PACE meeting. The key points of their submissions 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 (50 years).
Population	Patients with primary refractory or early relapse (≤ 12 months of first-line therapy) DLBCL and HGBL who are intended for transplant.
Comparators	The comparator considered in the economic evaluation was standard of care (SoC), which the company defined as salvage chemotherapy followed by HDT-auto-SCT in responders. The analysis considered a 'basket' of salvage chemotherapy regimens used in ZUMA-7.
Model description	A *de novo* model was developed using a partitioned survival analysis framework. The model structure was comprised of five health states. Three 'core' health states captured a patient's health status ('event-free', 'post-event', and 'death'). To account for differences in the costs and health effects accrued by patients whilst they are receiving active treatment for their disease, the 'event-free' state, this was subdivided into 'on treatment' and 'on next treatment' substates. Similarly, the 'post-event' state was subdivided into 'on next treatment' and 'off treatment' substates. All patients start in the 'event-free' health state and can transition to any of the other 'core' health states at any point in time. After experiencing an 'event', the only transition available to patients was to the 'death' health state.
Clinical data	The clinical data used to inform model parameters was mostly consistent with that reported in ZUMA-7.[9-11]

	The proportion of patients receiving bridging therapy and the type of therapy used was informed by clinical expert feedback and assumed to consist of one cycle of polatuzumab vedotin in combination with bendamustine and rituximab.
Extrapolation	To extrapolate EFS, OS, and time-to-next-treatment (TTNT) data collected during ZUMA-7 to the time horizon used in the economic evaluation, the company used mixture-cure models. This assumes the overall population can be 'split' into two separate groups: those who are cured of their disease (experience long-term remission) and those who are uncured of their disease (do not experience long-term remission). For EFS the company used a log-logistic model in the axicabtagene ciloleucel arm and an exponential curve in the SoC arm. A generalised gamma function was used across both arms to model OS and a log-logistic curve was used across both arms to extrapolate TTNT. The estimated cure fractions were listed as academic in confidence at the time of SMC's review and so cannot be reported here.
Quality of life	For the 'event-free' health state, health utility was estimated using EQ-5D-5L questionnaire data collected at specific time points during ZUMA-7. For the 'post-event' health state, health utility was estimated using EQ-5D-5L questionnaire data collected during the ZUMA-1 study conducted in adult patients with refractory aggressive non-Hodgkin's lymphoma.[10, 12] Disutilities associated with receiving active treatment and AEs were also accounted for. The model assumed that patients estimated to be event-free at 5 years have a quality of life equivalent to the general population level for their age and sex.
Costs and resource use	Medication related costs for patients receiving axicabtagene ciloleucel included: acquisition of bridging therapy, lymphodepleting (conditioning) chemotherapy, and axicabtagene ciloleucel, and administration for all medications received. Base case results include leukapheresis as an NHS cost. A scenario is presented where leukapheresis costs are excluded as an NHS cost. Analogous costs for SoC included: acquisition of salvage chemotherapy regimens, HDT, and auto-SCT (responders only), and administration for all medications received. The cost of different types of subsequent therapies received by patients were also accounted for using a single 'one-off' cost. Other healthcare resource use included in the analysis constituted resources associated with ongoing monitoring for patients (e.g. general practitioner and district nurse appointments, radiographic imaging, outpatient appointments with consultants, laboratory based tests, etc) and end of life care.
PAS	A Patient Access Scheme (PAS) was submitted by the company. The PAS was not accepted by the Patient Access Scheme Assessment Group (PASAG) therefore the cost-effectiveness estimates based on the PAS were not considered by SMC as part of the economic case. The results presented do not take account of the PAS for tisagenlecleucel, pembrolizumab, nivolumab, polatuzumab and axicabtagene ciloleucel in the third-line setting, which were subsequent therapies used in the model, but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for tisagenlecleucel, pembrolizumab, nivolumab, and polatuzumab due to commercial confidentiality and competition law issues.

6.2. Results

The base case economic results at list price for all medicines indicate that treatment with axicabtagene ciloleucel is more costly but more effective than treatment with SoC. When the PAS discounts available on subsequent treatments are not considered, the incremental cost effectiveness ratio (ICER) is £69,534 per quality adjusted life year (QALY) gained.

Disaggregated analysis of total cost figures for axicabtagene ciloleucel and the SoC indicate that the majority of the increased costs associated with axicabtagene ciloleucel are due to its acquisition price, the impact of which is reduced by a reduction in the cost of subsequent therapies. Incremental QALYs for axicabtagene ciloleucel relative to the SoC are composed of a larger number of years in the 'event-free' health state, which is reduced by a lower number of years spent in the 'post-event' health state.

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

6.3. Sensitivity analyses

The submitting company conducted a range of different types of sensitivity analyses, which highlighted particular areas of uncertainty regarding economic results.

A selection of these results at list price for all medicines are included in Table 6.3.

Table 6.3: Scenario analyses using list prices for all medicines

	Parameter	Base Case	Scenario	ICER (£/QALY)
	Base case			69,534
1	Time horizon	50 years	10 years	149,069
2			20 years	85,561
3	Extrapolation of EFS **(axicabtagene ciloleucel only)**	**Approach:** Mixture-cure model using log-logistic distribution **Cure fraction:** AiC	**Approach:** Mixture-cure model using generalised gamma distribution **Cure fraction**: AiC	68,689
4	Extrapolation of OS **(axicabtagene ciloleucel only)**	**Approach:** Mixture-cure model using generalised gamma distribution **Cure fraction:** AiC	**Approach:** Mixture-cure model using Weibull distribution **Cure fraction:** AiC	66,796
5			**Approach:** Mixture-cure model using log-logistic distribution **Cure fraction:** AiC	124,963
6	Proportion of patients receiving axicabtagene ciloleucel at 3-L **(SoC only)**	59% of patients alive at 3-L stage	51% of patients alive at 3-L stage	84,916
7			67% of patients alive at 3-L stage	54,151
8	Data source for 'post-event' health state utility value	ZUMA-1 study	JULIET study[13]	68,533
9	Incorporating disutility associated with receiving treatment	Include disutility for patients who experience adverse events	Exclude disutility for patients who experience adverse events	69,438

10	Incorporating re-treatment costs for axicabtagene ciloleucel	Exclude	Include total cost of treatment	80,477
11			Include administration only	69,776
12	Leukapheresis costs	Include as NHS costs	Exclude as NHS costs	68,727

Abbreviations: ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life-years; AiC = Academic in confidence; EFS = event-free survival; OS = overall survival; SoC = standard of care; HRQoL = health-related quality-of-life; 3-L = third-line

6.4. Key strengths

- The ZUMA-7 study provides clinical data comparing the efficacy of axicabtagene ciloleucel versus a comparator that appears to constitute SoC in the patient population within the context of NHS Scotland. The availability of such 'direct evidence' to inform the economic evaluation reduces uncertainty regarding the influence of confounding variables on relative efficacy, which are a concern when clinical data is drawn from multiple different sources ('indirect evidence').
- HRQoL data from ZUMA-7 using the EQ-5D-5L questionnaire (the preferred method for SMC submissions) was available to inform the quality of life experienced by patients in the 'event-free' health state of the economic model.

6.5. Key uncertainties

- The follow up period of ZUMA-7 is relatively short compared to the time horizon over which the economic evaluation is conducted (50 years). The implications of this in terms of economic results are that clinical outcomes require a significant degree of extrapolation, introducing uncertainty in economic results. The impact of this uncertainty can be viewed in scenarios 3-5 above where alternative methods for extrapolating data from ZUMA-7 for axicabtagene ciloleucel are used.
- The proportion of patients in the axicabtagene ciloleucel and SoC groups receiving different types of therapy in the 'post-event' health state was based on data from ZUMA-7 and validated with clinical expert feedback. Sensitivity analysis around the company's base case assumption regarding the proportion of patients in the SoC group receiving CAR-T therapies at a later line of treatment shows a significant impact on economic results (see scenarios 6 and 7). A larger proportion of patients in this group receiving CAR-T therapies improves the cost-effectiveness of axicabtagene ciloleucel due to the high cost of these therapies. However, it should be noted that these scenarios did not alter health outcomes, which would also likely be influenced by subsequent treatment choice.
- The submitting company noted that a small number of patients in the axicabtagene ciloleucel group received axicabtagene ciloleucel re-treatment. Analysis suggests that accounting for the cost of re-treatment for these patients could have a significant impact on results depending on whether this constitutes only administration costs or total treatment costs (see scenarios 10 and 11). The company has argued that re-treatment would be unlikely in Scottish practice and so exclusion of the retreatment costs were appropriate.

7. Conclusion

The Committee considered the benefits of axicabtagene ciloleucel in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for a substantial improvement in quality of life was satisfied. In addition, as axicabtagene ciloleucel is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee was unable to accept axicabtagene ciloleucel for use in NHSScotland.

8. Guidelines and Protocols

The European Society for Medical Oncology published in August 2015 'Recommended treatment strategies in DLBCL >2 relapse/progress'.[6]

In 2016 the British society for haematology published guidelines for the management of DLBCL.[7]

In 2016 the National Institute for Health and Care Excellence published guidance on Non-Hodgkin's lymphoma: diagnosis and management (NG52).[5]

The National Comprehensive Cancer Network (NCCN) published in October 2023: NCCN Clinical Practice Guidelines in Oncology - B-Cell Lymphomas, Version 6.2023.[8]

In 2022, the European Society for Blood and Marrow Transplantation (EBMT) published recommendations for heamatopoietic cell transplantation for haemotological diseases. [12]

9. Additional Information

9.1. Product availability date

19 December 2022

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per course (£)
Axicabtagene ciloleucel	A single intravenous dose with 1 x 10^6 to 2 x 10^6 CAR-positive viable T cells per kg of body weight; maximum of 2 × 10^8 CAR-positive viable T cells for patients ≥100 kg	**280,451**

Costs from eMC Dictionary of Medicines and Devices Browser on 03 November 2023.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The company estimates that there will be around 77 patients eligible for treatment with axicabtagene ciloleucel in year one rising to 79 in year five.

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

References

1. Gilead Sciences Ltd. Yescarta 0.4 – 2 × 10^8 cells dispersion for infusion - summary of product characteristics (SPC). Last updated: July 2023. Available at: www.medicines.org.uk.
2. Olszewski AJ, Kurt H, Evens AM. Defining and treating high-grade B-cell lymphoma, NOS. Blood. 2022;140(9):943-54. 10.1182/blood.2020008374
3. Lymphoma Action. Non-Hodgkin lymphoma. 2023. Available at: https://lymphoma-action.org.uk/types-lymphoma/non-hodgkin-lymphoma.
4. The European Medicines Agency (EMA) European Public Assessment Report. Yescarta (axicabtagene ciloleucel) variation assessment. 15 September 2022. EMA/804955/2022. Available at: http://www.ema.europa.eu.
5. National Institute for H, Care E. Non-Hodgkin's lymphoma: diagnosis and management (NG52). 2016 [cited; Available from: https://www.nice.org.uk/guidance/ng52/evidence.
6. Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v116-25. Epub 2015/09/01.
7. Chaganti S, Illidge T, Barrington S, Mckay P, Linton K, Cwynarski K, et al. Guidelines for the management of diffuse large B-cell lymphoma. British Journal of Haematology. 2016;174(1):43-56.
8. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology - B-Cell Lymphomas, Version 6.2023 published in October 2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf.
9. Locke FL, Miklos DB, Jacobson CA, Perales MA, Kersten MJ, Oluwole OO*, et al.* Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med. 2022;386:640-54. Epub Dec 11. 10.1056/NEJMoa2116133
10. Westin JR, Oluwole OO, Kersten MJ, Miklos DB, Perales MA, Ghobadi A*, et al.* Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma. N Engl J Med. 2023. Epub 2023/06/05. 10.1056/NEJMoa2301665
11. Westin JR, Oluwole OO, Kersten MJ, Miklos DB, Perales MA, Ghobadi A*, et al.* Primary Overall Survival Analysis of the Phase 3 Randomized ZUMA-7 Study of Axicabtagene Ciloleucel Versus Standard-of-Care Therapy in Relapsed/Refractory Large B-Cell Lymphoma. ASCO Annual Meeting. Chicago, IL: US; 2023.
12. Jacobson CA, Locke FL, Ghobadi A, Miklos DB, Lekakis LJ, Oluwole OO*, et al.* Long-term (4- and 5-year) overall survival in ZUMA-1, the pivotal study of axicabtagene ciloleucel in patients with refractory large B-cell lymphoma. ASH Annual Meeting. Virtual & Atlanta, GA: USA; 2021.
13. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP*, et al.* Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. New England Journal of Medicine. 2018;380(1):45-56. 10.1056/NEJMoa1804980
12. Snowden JA, Sánchez-Ortega I, Corbacioglu S, et al. Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2022. Bone Marrow Transplant. 2022;57(8):1217-1239. doi:10.1038/s41409-022-01691-w

This assessment is based on data submitted by the applicant company up to and including 15 December 2023.

**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.

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.