MSAC Application 1722

Axicabtagene ciloleucel (Yescarta®) for relapsed or refractory large B-cell lymphoma

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Email: hta@health.gov.au
Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant):
Corporation name: Gilead Sciences Pty Limited
ABN: **REDACTED**
Business trading name: Gilead Sciences Pty Limited

Primary contact name: REDACTED

Primary contact numbers
Business: **REDACTED**
Mobile: **REDACTED**
Email: **REDACTED**

Alternative contact name: REDACTED

Alternative contact numbers
Business: **REDACTED**
Mobile: **REDACTED**
Email: **REDACTED**

2. (a) Are you a consultant acting on behalf on an applicant?

☐ Yes
☒ No

(b) If yes what is the Applicant(s) name that you are acting on behalf of?

N/A

3. (a) Are you a lobbyist acting on behalf of an Applicant?

☐ Yes
☒ No

(b) If yes, are you listed on the Register of Lobbyists?

N/A

(c) Have you engaged a consultant on your behalf?

☐ Yes
☒ No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

4. Application title

Axicabtagene ciloleucel (Yescarta®) for relapsed or refractory large B-cell lymphoma (LBCL)

5. Provide a succinct description of the medical condition relevant to the proposed service

Large B-cell lymphoma (LBCL) is a heterogeneous collection of clinicopathological entities that are subtypes of non-Hodgkin's lymphoma. LBCL accounts for roughly one third of all cases of non-Hodgkin's lymphoma. Included in the LBCL subtype are: diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL), high grade B-cell lymphoma (HGBCL), transformed follicular lymphoma (TFL) and T-cell/histiocyte rich large B-cell lymphoma. DLBCL is the most common subtype of LBCL, accounting for approximately 80% of the cases of LBCL. (Sehn 2021[1])

Patients typically present with progressive lymphadenopathy, extranodal disease or both and require therapy. Diagnosis of LBCL relies on a detailed examination of tumour tissue, best achieved with an excisional biopsy specimen evaluated by an expert haematopathologist. In addition to morphologic characteristics, an accurate lymphoma classification requires specialised tests, including immunohistochemistry, flow cytometry, fluorescence *in situ* hybridization (FISH), and molecular testing. (Sehn 2021[1])

Despite the advanced stage of disease at presentation in most patients diagnosed with LBCL, up to 60% of patients can achieve long-term remission of disease with a first-line treatment regimen of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) immunochemotherapy (Coiffier 2010[2], Sehn 2021[1]). However, patients with treatment failure after R-CHOP often have a poor outcome. These patients have a high and urgent unmet clinical need for improved treatment alternatives.

6. Provide a succinct description of the proposed medical service

Axicabtagene ciloleucel is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell product.

CAR T-cell therapy is a type of immunotherapy in which a patient's T-cells (immune cells with anticancer activity) are collected and genetically modified in the laboratory to recognise cancer cells that express CD19 on their surface. The modified T-cells are expanded to several million and the modified cells are then infused back into the patient, where they target and kill cancer cells.

Further information on axicabtagene ciloleucel is provided in Part 6b of this application.

7. (a) Is this a request for MBS funding?

☐ Yes
☒ No

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

N/A

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service/technology:

(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

N/A

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

☐ A new item which also seeks to allow access to the MBS for a specific health practitioner group
☐ A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
☐ A new item for a specific single consultation item
☐ A new item for a global consultation item(s)

(f) Is the proposed service seeking public funding other than the MBS?

☒ Yes
☐ No

(g) If yes, please advise:

The Commonwealth and the States currently jointly fund various CAR T-cell therapies as Highly Specialised Therapies under the Addendum to the National Health Reform Agreement 2020-2025 (NHRA). This application proposes that the same funding mechanism be used to fund axicabtagene ciloleucel when used in patients with relapsed or refractory LBCL.

8. What is the type of medical service/technology?

☐ Therapeutic medical service
☐ Investigative medical service
☐ Single consultation medical service
☐ Global consultation medical service
☐ Allied health service
☐ Co-dependent technology
☒ Hybrid health technology

9. For investigative services, advise the specific purpose of performing the service *(which could be one or more of the following)*:

N/A

10. Does your service rely on another medical product to achieve or to enhance its intended effect?

☒ Pharmaceutical / Biological
☐ Prosthesis or device
☐ No

11. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

☒ Yes
☐ No

Bridging therapy

Bridging therapy may be given to certain patients requiring stabilisation of disease during the manufacturing process of axicabtagene ciloleucel. Bridging therapy consists of corticosteroids, most commonly dexamethasone, however other corticosteroids such as methylprednisolone, prednisone and prednisolone may be used. All of the listed corticosteroids are available as unrestricted benefits on the PBS.

Lymphodepletion

Lymphodepleting chemotherapy is administered to patients prior to infusion with axicabtagene ciloleucel. A combination of fludarabine (30 mg/m^2/day) and cyclophosphamide (500 mg/m^2/day) is given to patients on days 5, 4 and 3 prior to infusion. Both treatments are available as unrestricted benefits on the PBS.

Management of serious adverse reactions

As with other CAR T-cell therapies, corticosteroids and tocilizumab may be administered to patients requiring management of cytokine release syndrome (CRS). Tocilizumab is not reimbursed on the PBS for the management of CRS.

As with other CAR T-cell therapies, immunoglobulin was administered to some patients in the key ZUMA-7 trial. Immunoglobulin is funded via the National Blood Authority.

(b) If yes, please list the relevant PBS item code(s):

Dexamethasone:	1292B, 2507Y
Prednisolone:	1916W, 1917X, 3152X
Prednisone:	1934T, 1935W, 1936X
Methylprednisolone:	11739W, 5263B, 5264C
Fludarabine:	4393F
Cyclophosphamide:	4327R
Tocilizumab:	not reimbursed for management of CRS
Immunoglobulin:	Funded through the National Blood Authority (see https://www.blood.gov.au/national-product-list [Last accessed: 25 Feb 2022])

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

☐ Yes (please provide PBAC submission item number below)
☒ No

(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

N/A

12. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

☐ Yes
☐ No

(b) If yes, please provide the following information (where relevant):

N/A

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

N/A

(d) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?

N/A

(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

N/A

13. Please identify any single and / or multi-use consumables delivered as part of the service?

As discussed in Part 6b of this application, there are a number of stages in the process of delivering axicabtagene ciloleucel that require the use of consumables e.g., collection of leucocytes from the patient by leukapheresis, administration of bridging therapy, administration of lymphodepleting therapy, infusion of axicabtagene ciloleucel.

Consumables that are likely to be required include: gloves, masks, sterile alcohol wipes, sterile field procedural mats, spill kits, labels, syringes, needles, gauze, plasma collection sets, collection containers, adhesive tapes, IV administration sets, filters, IV fluids (e.g., normal saline).

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

14. (a) If the proposed medical service involves use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer, or any other type of therapeutic good, please provide details.

Type of therapeutic good: Class 4 biological product
Manufacturer's name: Kite Pharma, a Gilead Company
Sponsor's name: Gilead Sciences Pty Ltd

(b) Has it been listed on the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)? If the therapeutic good has been listed on the ARTG, please state the ARTG identification numbers, TGA-approved indication(s), and TGA-approved purpose(s).

Axicabtagene ciloleucel is currently listed on the ARTG as follows:

ARTG ID: 329770

TGA approved indications:
YESCARTA is a genetically modified autologous immunocellular therapy for the treatment of relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.

REDACTED

(c) If a medical device is involved, has the medical device been classified by TGA as a Class III OR Active Implantable Medical Device (AIMD) under the TGA regulatory scheme for devices?

☐ Class III
☐ AIMD
☒ N/A

(d) Is the therapeutic good classified by TGA for Research Use Only (RUO)?

☐ Yes
☒ No

15. (a) <u>If not listed on the ARTG</u>, is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

☐ Yes (If yes, please provide supporting documentation as an attachment to this application form)
☐ No

(b) If the therapeutic good is <u>not ARTG listed</u>, is the therapeutic good in the process of being considered by TGA?

A revised indication has been proposed for axicabtagene ciloleucel as detailed in the response given to beyond the one listed above in Q14 (b).

(c) If the therapeutic good is NOT in the process of being considered by TGA, is an application to TGA being prepared?

N/A

PART 4 – SUMMARY OF EVIDENCE

16. Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At 'Application Form lodgement', please do not attach full text articles; just provide a summary.

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1	Phase 3, randomised, open-label, multicentre study	ZUMA-7 trial NCT03391466 Locke et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med. 2022;386(7):640-654. DOI: 10.1056/NEJMoa2116133	Evaluation of the comparative efficacy and safety of axicabtagene ciloleucel (N=180) versus standard of care# (N=179) in patients with LBCL that were refractory to or had relapsed within 12 months following frontline chemotherapy treatment. Over a median follow up of 25 months, compared to SoC, axicabtagene ciloleucel resulted in a significant improvement in event-free survival (8.3 months versus 2.0 months). The response rate was 83% in axicabtagene ciloleucel-treated patients and 50% in the standard-care group. The safety profile of axicabtagene ciloleucel was consistent with previous experience.	https://www.nejm.org/doi/full/10.1056/NEJMoa2116133 [Last accessed: 28 Feb 2022]	February 17, 2022

Standard of care consisted of platinum-based salvage chemoimmunotherapy followed by myeloablative high dose chemotherapy with rescue by means of autologous stem-cell transplant (HDT + auto-SCT) in those that responded to salvage chemoimmunotherapy (only 36% of patients treated with platinum-based salvage chemoimmunotherapy received HDT + auto-SCT in the control arm of the ZUMA-7 trial)

17. **Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application). Do not attach full text articles; this is just a summary.**

None identified

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

18. List all appropriate professional bodies/organisations representing the health professionals who provide the service. For MBS-related applications ONLY, please attach a brief 'Statement of Clinical Relevance' from the most relevant college/society.

- Haematology Society of Australia and New Zealand (HSANZ)
- The Australian Leukaemia and Lymphoma Group (ALLG)
- Australia and New Zealand Transplant and Cellular Therapies society (ANZTCT)

19. List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):

The same groups as above.

20. List the consumer organisations relevant to the proposed medical service (noting there is NO NEED to attach a support letter at the 'Application Lodgement' stage of the MSAC process):

- Lymphoma Australia
- Rare Cancers Australia
- Snowdome Foundation

21. List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:

Similar products that have potential for use as a second-line treatment for patients with relapsed or refractory LBCL include:

- Tisagenlecleucel (KYMRIAH®), sponsored by Novartis Pharmaceuticals Australia Pty Ltd, is currently reimbursed as a third-line treatment for LBCL and has been trialled in the second line setting (BELINDA trial[3]). In contrast to the ZUMA-7 trial for axicabtagene ciloleucel, the BELINDA trial found that tisagenlecleucel was not superior to standard salvage therapy in the second line setting.
- Lisocabtagene maraleucel (BREYANZI®), sponsored in the USA by Juno Therapeutics, Inc. (a Bristol-Myers Squibb Company), is currently not registered for use in Australia but has been trialled as a second-line treatment for LBCL (TRANSFORM trial[4]).

At the time of the preparation of this application, no applications to MSAC requesting funding for either of these treatments as second-line treatments for LBCL appear to have been lodged.

22. Nominate two experts that can be contacted about the proposed medical service, and current clinical management of the condition:

Name of expert 1:	**REDACTED**
Telephone number(s):	**REDACTED**
Email address:	**REDACTED**
Justification of expertise:	**REDACTED**

Name of expert 2:	**REDACTED**
Telephone number(s):	**REDACTED**
Email address:	**REDACTED**
Justification of expertise:	**REDACTED**

PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

23. Define the medical condition, including providing information on the natural history of the condition and a high level summary of associated burden of disease (in terms of both morbidity and mortality).

As discussed in response to Question 5, LBCL is a heterogenous group of lymphomas with different morphologies, pathologies, gene profiles and clinical characteristics.

The 2016 World Health Organisation (WHO) classification of lymphoid neoplasms updated and defined the appropriate identification of the various entities included in the LBCL classification (Swerdlow 2016[5]). Entities in the LBCL classification include:

- DLBCL, not otherwise specified (NOS), which can be further categorised into two distinct molecular subgroups determined by the type of B-cell DLBCL has grown from: germinal centre B-cell-like (GCB) and activated B-cell-like (ABC)
- high-grade B-cell lymphoma (HGBCL), with or without *MYC* and *BCL2* and/or *BCL6* rearrangement
- DLBCL arising from follicular lymphoma
- primary cutaneous DLBCL
- Epstein-Barr virus positive DLBCL
- T-cell/histiocyte rich LBCL
- primary mediastinal B-cell lymphoma (PMBCL)
- DLBCL associated with chronic inflammation

DLBCL (NOS) is the most common subtype of LBCL, accounting for more than 80% of the cases of LBCL (Sehn 2021[1]).

Typical presentation of DLBCL involves rapidly progressive lymphadenopathy (Sehn 2021[1], Li 2018[6]). Typical B symptoms (fatigue, weight loss, night sweats, etc.) are observed in roughly one third of patients with DLBCL (Armitage 1998[7]).

Table 1 summarises the diagnostic and clinical features of each of the LBCL entities listed above. A more detailed list is provided by Sehn 2021[1].

Table 1: Diagnostic and clinical characteristics of some LBCL subtypes

WHO denomination	Diagnostic features	Clinical features
DLBCL, NOS	Diffuse proliferation of medium or large lymphoid B cells typically expressing CD19, CD20, CD22, CD79a, PAX5 and surface or cytoplasmic immunoglobulin	Median age: 65-70 years, most commonly nodal presentation but 30-40% of cases are primary extranodal; varying prognosis
HGBCL with or without *MYC* and *BCL2* and/or *BCL6* rearrangement	Variable morphology, including DLBCL, B-cell lymphoma unclassifiable, and blastoid features	Frequently aggressive clinical presentation; higher risk of CNS involvement; poor prognosis
DLBCL arising from follicular lymphoma	Transformation (from FL to DLBCL) is confirmed by biopsy and defined by increased numbers of large cells which eradicate the follicular architecture	Generally aggressive disease; varying prognosis
Primary cutaneous DLBCL	Typically ABC subtype, frequent mutation of *MYD88*	Typically in elderly patients and women, presents with skin

WHO denomination	Diagnostic features	Clinical features
		nodules in lower legs; poor prognosis
EBV positive DLBCL	Variable histologic features, EBV detectable in tumour and frequently serum	Typically in patients older than 50 years, extranodal involvement common; varying prognosis
T-cell/histiocyte rich LBCL	Few large B cells embedded in a background of T cells and histiocytes	Commonly found in middle-aged men, advanced stage with extranodal involvement; poor prognosis
PMBCL	Putative thymic B-cell origin; medium-to-large B cells, distinctive phenotype (CD30, CD23, PDL1, PDL2), frequent 9p21 amplification	Typically in young adults, female predominance; varying prognosis
DLBCL associated with chronic inflammation	Similar to DLBCL, NOS but strongly associated with EBV	Involving pleural cavity or other sites such as bone and joints, male predominance; poor prognosis

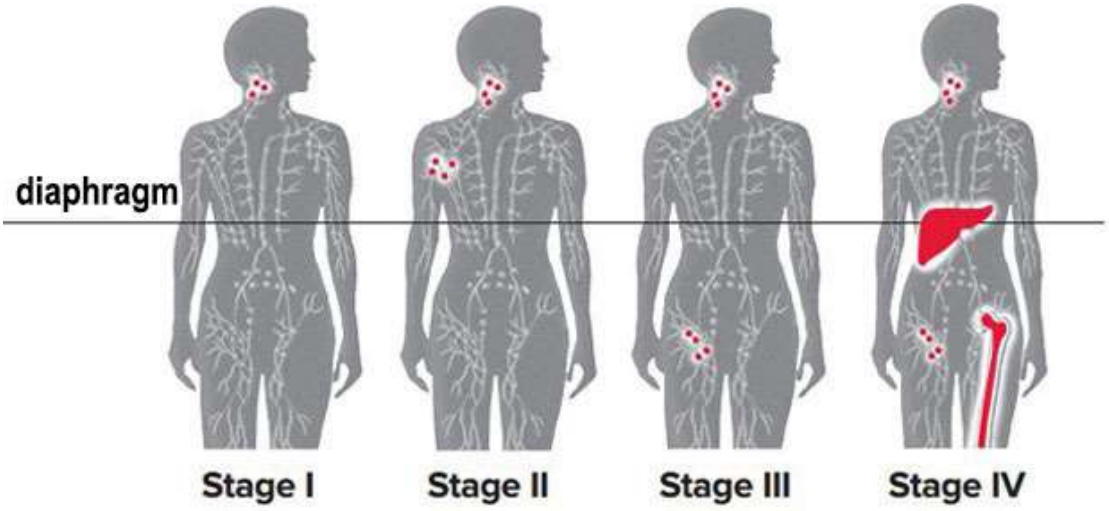
Source: Abridged version of Table 1 from Sehn 2021[1], Casulo 2015[8] for DLBCL arising from follicular lymphoma

Abbreviations: ABC = activated B-cell-like; DLBCL = diffuse large B-cell lymphoma; EBV = Epstein-Barr virus; FL = follicular lymphoma; HGBCL = High-grade B-cell lymphoma; NOS = not otherwise specified; PMBCL = primary mediastinal large B-cell lymphoma

Disease staging of patients with non-Hodgkin's lymphoma is based on a consideration of the location and extent of disease (Cheson 2014[9]), as summarised in Figure 1.

The majority of patients with DLBCL are diagnosed with advanced stage disease (Stage III-IV) (Lymphoma Australia[10]).

Figure 1: Diagrammatic representation of stages of non-Hodgkin's lymphoma



Source: Leukemia & Lymphoma Society[11]

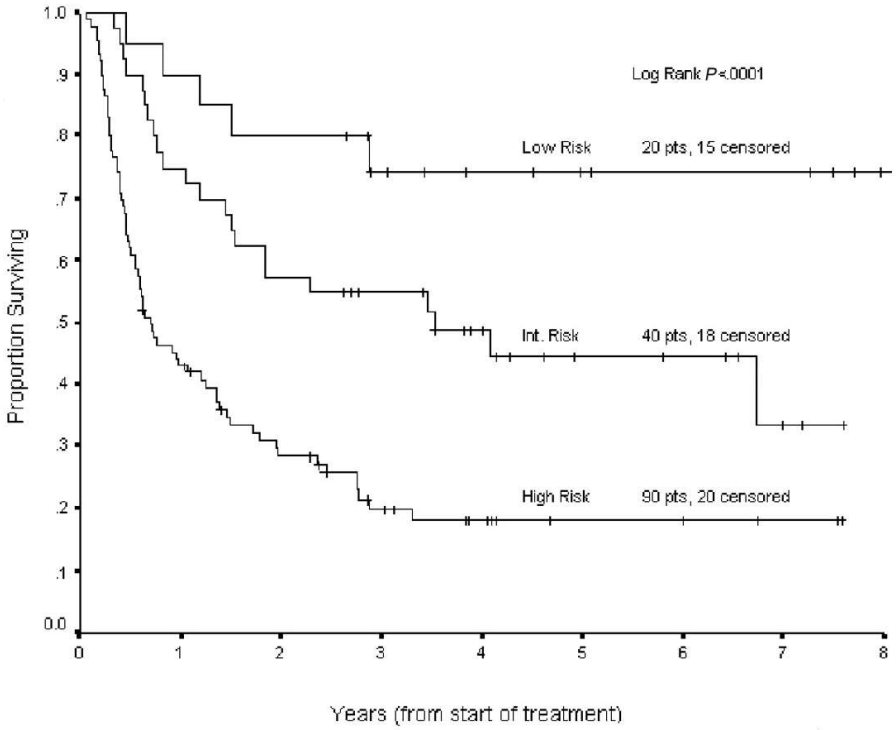
Response to frontline therapy of DLBCL with R-CHOP results in sustained disease-free survival in approximately 60% of patients (Coiffier 2010[2], Sehn 2021[1]). However, current treatment options for the 30-40% of patients who relapse or are refractory to frontline treatment are considered inadequate. Patients who relapse or are refractory to frontline treatment who are candidates for further therapy will typically be treated with platinum-based chemoimmunotherapy. Unfortunately, only a minority of patients respond to salvage chemoimmunotherapy and are candidates for potentially curative treatment with myeloablative high dose chemotherapy followed by rescue with autologous stem cell transplantation (HDT + auto-SCT). Approximately 35% to 40% of those treated with salvage chemoimmunotherapy go on to receive HDT + auto-SCT[12,13]. However, a substantial proportion of patients are not cured by this approach. The prognosis of these patients as well as that of patients who cannot undergo transplantation is poor (Li 2018[6]). Prior to availability of CAR T-cell therapy as a third-line treatment, survival following relapse, re-treatment or progression was approximately 13 months (Maurer 2014[14]).

For DLBCL, the age-adjusted International Prognostic Index at initiation of second-line therapy (sAAIPI) is available to predict progression-free survival and overall survival for patients with relapsed or primary refractory DLBCL (Hamlin 2003[15]). The Index uses three factors to determine prognosis, awarding one point for each factor met:

- Elevated lactate dehydrogenase (LDH) levels (greater than the upper limit of normal per local laboratory reference range)
- Disease stage III or IV
- ECOG performance status greater than 1

Index scores of 0, 1, 2 or 3 on this instrument, which correlate to a low (0), intermediate (1), and high risk disease (2-3), respectively are possible (Hamlin 2003[15]). Estimates of survival by index score is shown in Figure 2. Patients in the key trial comparing standard of care to axicabtagene ciloleucel in patients with LBCL who have relapsed or are refractory to frontline treatment (ZUMA-7) were stratified by sAAIPI risk.

Figure 2: Intention-to-treat analysis of overall survival in patients relapsing or refractory to first-line treatment, stratified by the age-adjusted International Prognostic Index at the initiation of second-line therapy (sAAIPI risk group)



Source: Hamlin 2003[15] Figure 3B

24. Specify the characteristics of patients with (or suspected of having) the medical condition, who would be eligible for the proposed medical service/technology (including details on how a patient would be investigated, managed and referred within the Australian health care system, in the lead up to being eligible for the service):

It is proposed that the current availability of axicabtagene ciloleucel, which permits use of axicabtagene ciloleucel as a third-line agent, be modified to also permit use of axicabtagene ciloleucel in the second-line setting, as follows:

Patients with confirmed relapsed or refractory large B-cell lymphoma (LBCL). Patients are required to have evidence of progressing disease despite treatment with at least one prior systemic therapy.

The population for whom reimbursement of axicabtagene ciloleucel is proposed is intended to be consistent with the eligibility criteria that were applied in recruiting patients to the ZUMA-7 pivotal trial.

Patients treated for LBCL will be in the care of an expert haematologist or haematologist-oncologist who will monitor patients following first-line chemoimmunotherapy for response and maintenance of a disease-free state. Should a patient be refractory to or relapse after first-line treatment, the specialist will be able to refer the patient to a qualified treatment centre that is qualified to deliver treatment with axicabtagene ciloleucel.

PART 6b – INFORMATION ABOUT THE INTERVENTION

25. Describe the key components and clinical steps involved in delivering the proposed medical service/technology:

Axicabtagene ciloleucel is a CAR T-cell product produced using a patient's own T-cells, making the product unique to each patient. A patient's T-cells are collected via a process called leukapheresis. The T-cells are genetically modified in a lab to express an anti-CD19 chimeric antigen receptor (CAR) which targets the lymphoma B-cells. Following modification and subsequent proliferation, the T-cells are infused back into the patient where they target and kill the lymphoma B-cells.

The manufacturing and treatment process are described in greater detail below.

Step 1: Leukapheresis

Leukocytes (white blood cells) are collected from the patient at their clinical centre. This is done by leukapheresis, whereby whole blood is withdrawn from the patient, leukocytes are extracted and then the remainder of the blood is transfused back into the patient. The collected white blood cells are then transported immediately to the axicabtagene ciloleucel manufacturing facility.

Step 2: Procurement of axicabtagene ciloleucel

The manufacturing process is undertaken in **REDACTED**. The manufacturing process involves isolation and activation of T-cells, genetic modification of T-cells to encode the CAR gene, and growth and expansion of engineered T-cells. The final product is washed, cryopreserved, and tested for identity, potency, and sterility. After meeting acceptance criteria, the product is transported back to the patient's qualified delivery centre in Australia using a validated cryo-shipper.

Step 3: Bridging therapy (if necessary)

Patients are monitored while the production of CAR T-cells is in progress. If necessary, patients may receive bridging therapy with corticosteroids (typically dexamethasone) to ensure the patient remains viable for infusion of axicabtagene ciloleucel.

Step 3: Lymphodepleting chemotherapy

Prior to infusion, patients are treated with low-dose lymphodepleting chemotherapy to eliminate the patient's lymphocytes and allow space for the T-cells to expand. Lymphodepleting chemotherapy consists of fludarabine (30 mg/m^2/day) plus cyclophosphamide (500 mg/m^2/day) for three days (on the fifth, fourth, and third day before the infusion of axicabtagene ciloleucel on Day 0).

Step 4: Treatment infusion

Axicabtagene ciloleucel is a single infusion product. Each bag for intravenous (IV) infusion contains a suspension of a patient's own genetically modified anti-CD19 CAR T-cells. Following infusion, patients require daily monitoring for at least 7 days to monitor for signs and symptoms of CRS or neurologic events.

26. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

Yes, axicabtagene ciloleucel (Yescarta®) is a registered class 4 biological product.

27. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

N/A

28. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency)?

Axicabtagene ciloleucel will be administered at tertiary public hospitals that have successfully completed Gilead's rigorous site qualification process to ensure all quality and safety requirements can be satisfied.

Patients will require daily monitoring for at least 7 days at the qualified healthcare/clinical facility following infusion for possible adverse events, such as CRS or neurologic events.

Patients are then instructed to remain within proximity of the qualified clinical facility for at least 4 weeks following infusion with axicabtagene ciloleucel.

29. If applicable, identify any healthcare resources or other medical services that would need to be delivered <u>at the same time</u> as the proposed medical service:

Bridging therapy may be administered to some patients in the period between the collection of cells and the infusion of axicabtagene ciloleucel. Bridging therapy may be required in patients who have a high disease burden to ensure that the patient remains viable to have axicabtagene ciloleucel infused. The most commonly administered bridging therapy in the key study was dexamethasone, which is PBS-listed as an unrestricted benefit.

A 3-day lymphodepleting chemotherapy regimen, consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day is administered on the 5th, 4th, and 3rd days (followed by 2 rest days) before axicabtagene ciloleucel infusion. Both chemotherapy drugs are listed on the PBS as unrestricted benefits.

Paracetamol 500 -1000 mg and diphenhydramine 12.5 mg should be administered approximately one hour prior to infusion with axicabtagene ciloleucel.

Axicabtagene ciloleucel is administered by IV infusion in an inpatient hospital setting, under the supervision of a haematologist or haematologist-oncologist.

Some patients may require administration of treatments following infusion of axicabtagene ciloleucel as supportive care and for management of adverse events (e.g., blood products, antiemetics, tocilizumab).

30. If applicable, advise which health professionals will primarily deliver the proposed service:

Haematologists and haematologist-oncologists.

31. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

N/A

32. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

As with other CAR T-cell therapies, it is proposed axicabtagene ciloleucel will only be able to be administered in qualified treatment centres. **REDACTED**

33. If applicable, advise what type of training or qualifications would be required to perform the proposed service, as well as any accreditation requirements to support service delivery:

Axicabtagene ciloleucel will be prescribed by physicians who are experienced in the treatment of patients with haematological malignancies. **REDACTED**

34. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select ALL relevant settings):

☐ Inpatient private hospital (admitted patient)
☒ Inpatient public hospital (admitted patient)
☐ Private outpatient clinic
☒ Public outpatient clinic
☐ Emergency Department
☐ Private consulting rooms - GP
☐ Private consulting rooms – specialist
☐ Private consulting rooms – other health practitioner (nurse or allied health)
☐ Private day surgery clinic (admitted patient)
☐ Private day surgery clinic (non-admitted patient)
☐ Public day surgery clinic (admitted patient)
☐ Public day surgery clinic (non-admitted patient)
☐ Residential aged care facility
☐ Patient's home
☐ Laboratory
☐ Other – please specify below

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

Patient's T-cells will be collected at an outpatient clinic via leukapheresis. Extracted apheresis material is then couriered to an offsite manufacturing facility **REDACTED**, and returned to Australia to the healthcare/clinical facility qualified by Gilead. Lymphodepleting chemotherapy with fludarabine and cyclophosphamide on the fifth, fourth, and third day before axicabtagene ciloleucel will be infused at an outpatient clinic. Axicabtagene ciloleucel will be administered at the qualified healthcare/clinical facility. Patients will require monitoring daily for at least 7 days at the qualified healthcare/clinical facility following infusion for possible adverse events such as CRS.

35. Is the proposed medical service intended to be entirely rendered in Australia?

☐ Yes
☒ No – please specify below

The delivery of axicabtagene ciloleucel will be at a healthcare/clinical facility in Australia qualified by Gilead, however the procurement of axicabtagene ciloleucel is undertaken off-shore **REDACTED**

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

36. Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service):

The main comparator for axicabtagene ciloleucel is the therapy most likely to be replaced by axicabtagene ciloleucel. Standard of care (SoC) in patients who are refractory to, or have relapsed after, first-line treatment with chemoimmunotherapy, ideally consists of salvage chemoimmunotherapy, collection of peripheral stem cells, myeloablative HDT and rescue by means of autologous stem cell

rescue (HDT + auto-SCT). However, only patients who demonstrate adequate disease response after salvage chemotherapy and for whom a sufficient number of stem cells have been collected go on to receive HDT + auto-SCT. As detailed in the response to Question 23, only 35% to 40% of those treated with salvage chemoimmunotherapy go on to receive HDT + auto-SCT. Although some patients are considered cured after treatment with HDT + SCT, a substantial proportion of patients are not cured by this approach. The prognosis of these patients as well as that of patients who cannot undergo transplantation is poor

Salvage chemoimmunotherapy typically consists of one of the following regimens:

- R-ICE (rituximab plus ifosfamide, carboplatin and etoposide)
- R-ESHAP (rituximab plus etoposide, methylprednisolone, cytarabine and cisplatin)
- R-GDP (rituximab plus gemcitabine, dexamethasone and cisplatin/carboplatin)
- R-DHAP (rituximab plus dexamethasone, high-dose cytarabine and cisplatin/oxaliplatin)

All of the above salvage chemoimmunotherapy regimens are available on the PBS for relapsed or refractory LBCL.

In patients who respond to treatment with one of the salvage chemoimmunotherapy regimens, treatment with myeloablative HDT followed by rescue with auto-SCT are the next recommended treatments (Sehn 2021[1]). High dose chemotherapeutic regimens include BEAM (carmustine, etoposide, cytarabine and melphalan) or CBV (cyclophosphamide, carmustine and etoposide) (Zahid 2017[16]). Myeloablative high dose chemotherapy is given to patients to condition them prior to auto-SCT.

37. Does the medical service (that has been nominated as the comparator) have an existing MBS item number(s)?

☐ Yes (please list all relevant MBS item numbers below)
☒ No

38. (a) Will the proposed medical service/technology be used in addition to, or instead of, the nominated comparator(s)?

☐ In addition to (i.e. it is an add-on service)
☒ Instead of (i.e. it is a replacement or alternative).If yes, please outline the extent to which the current service/comparator is expected to be substituted

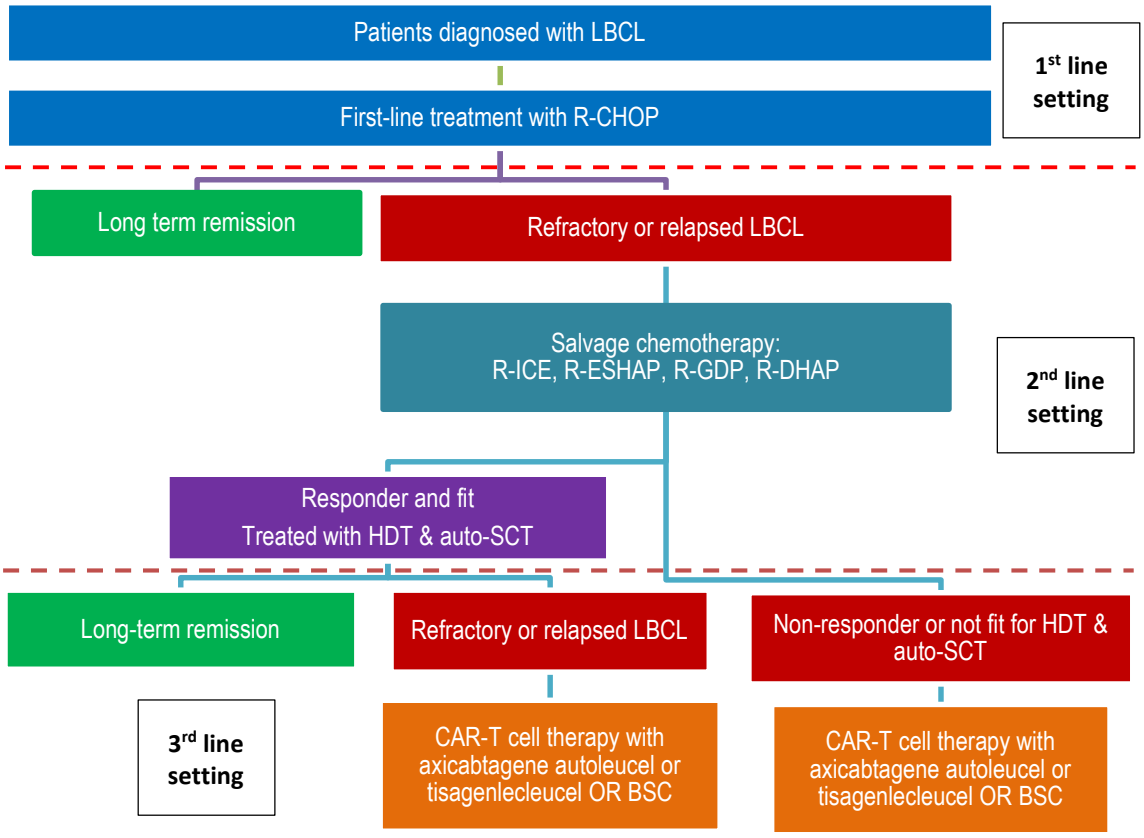
Axicabtagene ciloleucel will substitute for SoC in a substantial proportion of patients with LBCL who have relapsed after or are refractory to first-line treatment. Over time, axicabtagene ciloleucel is likely to become the standard of care in such patients. In addition to substituting for standard of care in the second-line setting, the ZUMA-7 trial demonstrates that there is also a reduced need for use of CAR T-cell therapies (tisagenlecleucel and axicabtagene ciloleucel) in the third line setting in the SoC arm.

PART 6c CONTINUED – INFORMATION ABOUT ALGORITHMS (CLINICAL MANAGEMENT PATHWAYS)

39. Define and summarise the CURRENT clinical management pathway (algorithm) that patients follow when they receive the COMPARATOR service (i.e. the landscape before the proposed service is introduced). An easy-to-follow flowchart is preferred, depicting the current clinical management pathway), but dot-points would be acceptable. Please include health care resources used in the current landscape (e.g. pharmaceuticals, diagnostics and investigative services, etc.).

Figure 3 summarises the clinical management pathway in the current scenario, where CAR T-cell therapies are not available for use in LBCL in the second-line setting.

Figure 3: Current management pathway for patients with LBCL in Australia

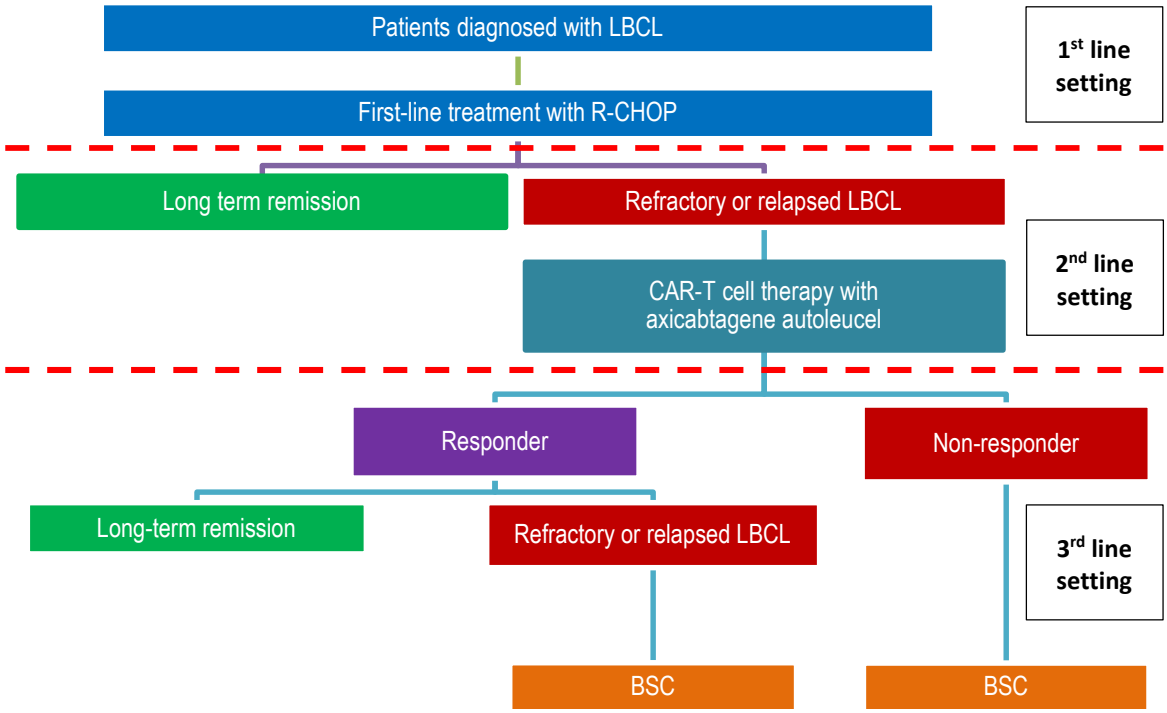


Abbreviations: BSC = best supportive care; CAR = chimeric antigen receptor; HDT = high-dose chemotherapy; LBCL = large B-cell lymphoma; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DHAP = rituximab plus dexamethasone, high-dose cytarabine and cisplatin/oxaliplatin; R-ESHAP = rituximab plus etoposide, methylprednisolone, cytarabine and cisplatin; R-GDP = rituximab plus gemcitabine, dexamethasone and cisplatin/carboplatin; R-ICE = rituximab plus ifosfamide, carboplatin and etoposide; SCT = stem cell transplant.

40. Define and summarise the PROPOSED clinical management pathway (algorithm) that patients would follow <u>after</u> the proposed service/technology is introduced, including variation in health care resources.

Figure 4 summarises the clinical management pathway in the proposed scenario, where axicabtagene ciloleucel is available for use in LBCL in the second-line setting. Availability of axicabtagene ciloleucel for patients with relapsed or refractory LBCL after first-line treatment would likely, over time, become the standard of care in such patients.

Figure 4: Proposed management pathway for patients with LBCL in Australia



Abbreviations: BSC = best supportive care; CAR = chimeric antigen receptor; LBCL = large B-cell lymphoma; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

<u>PART 6d – INFORMATION ABOUT CLINICAL OUTCOMES</u>

41. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

On the basis of results from the ZUMA-7 trial, conducted in patients with relapsed or refractory LBCL following first-line treatment, axicabtagene ciloleucel is superior to SoC (which involves salvage chemoimmunotherapy, and, in 35%-40% of patients, HDT and auto-SCT) in terms of event-free survival, proportion of patients achieving response to treatment, and overall survival.

When considering the treatment algorithm of patients with relapsed or refractory LBCL, it is claimed that use of axicabtagene ciloleucel in the second-line setting results in a reduction in the use of CAR T-cell therapies (tisagenlecleucel and axicabtagene ciloleucel) in the third-line setting.

The safety profile of axicabtagene ciloleucel, as observed in the ZUMA-7 trial, is consistent with the safety profile of axicabtagene ciloleucel as observed in other studies of axicabtagene ciloleucel (e.g., ZUMA-1 study) and real-world experience with this CAR-T therapy. From a comparative point of view, serious treatment-emergent adverse events were reported in a similar proportion of patients treated with axicabtagene ciloleucel and treated with SoC.

42. Please state what the overall clinical claim is:

Axicabtagene ciloleucel is superior to SoC in terms of effectiveness in patients with relapsed or refractory LBCL following first-line treatment. Axicabtagene ciloleucel induces durable remissions in a majority of patients with relapsed or refractory LBCL after first-line treatment. A key driver of the superiority of axicabtagene ciloleucel is that, with current SoC, only 35%-40% of patients receive potentially curative therapy with HDT + autoSCT. Due to its superior efficacy in the second-line setting, compared to SoC, there will also be reduced need for CAR T-cell therapies (tisagenlecleucel and axicabtagene ciloleucel) in the third-line setting.

Axicabtagene ciloleucel is non-inferior to SoC in terms of safety.

There is growing experience with the safety profile of axicabtagene ciloleucel. The safety of axicabtagene ciloleucel in patients with relapsed or refractory LBCL following first-line treatment is consistent with the safety profile of axicabtagene ciloleucel as observed in other studies of axicabtagene ciloleucel (e.g., ZUMA-1 study) and real-world experience with this CAR-T therapy. From a comparative point of view, serious treatment-emergent adverse events were reported in a similar proportion of patients treated with axicabtagene ciloleucel and treated with SoC.

43. List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

<u>Safety Outcomes:</u>

- incidence of adverse events (AEs) and serious adverse events (SAEs)
- incidence of events of special interest e.g.,
    - incidence of cytokine release syndrome (CRS)
    - incidence of infection and febrile neutropenia
    - incidence of cytopenia (neutropenia, thrombocytopenia, anaemia)
    - incidence of neurologic events (e.g., encephalopathy)

<u>Clinical Effectiveness Outcomes:</u>

- Proportion of patients administered definitive therapy (i.e., auto-SCT in the SoC arm and axicabtagene ciloleucel in the intervention arm)
- Objective response rate (ORR) and complete response rate (CRR)
- Duration of response
- Event-free survival (EFS)
- Progression-free survival (PFS)
- Time to next treatment
- Health-related quality of life (HRQoL)
- Overall survival
- Quality adjusted survival

<u>Other outcomes:</u>

- Percentage of patients having axicabtagene ciloleucel infused of those who underwent leukapheresis
- Time from collection (leukapheresis) to infusion of axicabtagene ciloleucel
- Healthcare resource use and associated costs (including pre- and post-infusion and those necessary for prevention and management of AEs), presented in both disaggregated and aggregated format
- Incremental cost per life-year gained
- Incremental cost per quality-adjusted life-year (QALY) gained
- Estimates of use and associated financial implications

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

44. Estimate the prevalence and/or incidence of the condition in the proposed population:

Lymphoma Australia[10] estimate that approximately 2,000 Australians are affected by DLBCL every year. If DLBCL represents approximately 80% of all cases of LBCL, then it can be estimated that there are approximately 2,500 cases of LBCL diagnosed each year.

REDACTED

45. Estimate the number of times the proposed medical service/technology would be delivered to a patient per year:

The proposed therapy involves the administration of a single infusion.

46. How many years would the proposed medical service/technology be required for the patient?

The proposed therapy involves the administration of a single infusion.

47. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

Gilead plans to analyse epidemiological data sources and conduct market research to provide accurate estimates of population size in the ADAR.

48. Estimate the anticipated uptake of the proposed medical service/technology over the next three years, factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors), as well as provide commentary on risk of 'leakage' to populations not targeted by the service.

The likely rate of uptake of axicabtagene ciloleucel in the population of patients with relapsed or refractory LBCL after first-line treatment is currently unknown however Gilead plans to conduct market research to estimate the likely uptake of axicabtagene ciloleucel in this setting. A detailed analysis of likely extent of use of axicabtagene ciloleucel will be presented in the ADAR that will be lodged with MSAC.

Given that strict eligibility criteria for access to axicabtagene ciloleucel in the second-line setting will apply, the risk of use beyond the proposed population is low. It is highly unlikely the product would be used in patients other than those for whom reimbursement is sought.

PART 8 – COST INFORMATION

49. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

The cost per supply of axicabtagene ciloleucel has not been determined at this point in time. The cost per supply of axicabtagene ciloleucel will be provided in the ADAR.

50. Specify how long the proposed medical service/technology typically takes to perform:

REDACTED

Once the delivered product, which arrives frozen, is thawed, axicabtagene ciloleucel is stable for up to 3 hours. The entire contents of the bag containing axicabtagene ciloleucel is administered within 30 minutes by either gravity or a peristaltic pump.

51. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and usage characteristics that defines eligibility for the medical service/technology.

N/A

52. If public funding is sought through an alternative (non-MBS) funding arrangement, please draft a service description to define the population and usage characteristics that defines eligibility for the service/technology.

Proposed item descriptor: Patients with relapsed or refractory large B-cell lymphoma (LBCL).
Fee: The cost per supply of axicabtagene ciloleucel has not been determined at this point in time.

PROPOSED PICO CRITERIA

Table 2 summarises the proposed key components of the PICO criteria to be addressed in a ADAR that seeks to provide an answer to the fundamental research question of:

> *What is the comparative safety, effectiveness and cost-effectiveness of axicabtagene ciloleucel in patients with confirmed relapsed/refractory large B-cell lymphoma (LBCL)?*

Table 2: Summary of proposed PICO

Component	Description
Population	Patients with confirmed relapsed/refractory large B-cell lymphoma (LBCL)
Intervention	Axicabtagene ciloleucel
Comparator	Standard of care consisting of salvage chemotherapy ideally followed by myeloablative high-dose chemotherapy and stem cell rescue by means of an autologous stem cell transplant. However, only patients who demonstrate adequate disease response after salvage chemotherapy and for whom a sufficient number of stem cells have been collected are able to receive HDT and an auto-SCT.

Outcomes	<u>Clinical Effectiveness:</u>
	• Proportion of patients administered definitive therapy (i.e., auto-SCT in the SoC arm and axicabtagene ciloleucel in the intervention arm)
	• Objective response rate (ORR) and complete response rate (CRR)
	• Duration of response
	• Event-free survival (EFS)
	• Progression-free survival (PFS)
	• Time to next treatment
	• Health-related quality of life (HRQoL)
	• Overall survival
	• Quality adjusted survival
	
	<u>Clinical efficacy:</u>
	• Percentage of patients having axicabtagene ciloleucel infused of those who underwent leukapheresis
	• Time from collection (leukapheresis) to infusion of axicabtagene ciloleucel
	<u>Safety Outcomes:</u>
	• incidence of adverse events (AEs) and serious adverse events (SAEs)
	• incidence of events of special interest e.g.,
	  ○ incidence of cytokine release syndrome (CRS)
	  ○ incidence of infection and febrile neutropenia
	  ○ incidence of cytopenia (neutropenia, thrombocytopenia, anaemia)
	  ○ incidence of neurologic events (e.g., encephalopathy)
	
	<u>Cost-effectiveness:</u>
	• Healthcare resource use and associated costs (including pre- and post-infusion), presented in disaggregated and aggregated format
	• Incremental cost per life year gained (LYG)
	• Incremental cost per quality adjusted life year (QALY)
	
	<u>Financial implications:</u>
	• Number of patients suitable for treatment
	• Number of patients who receive treatment and associated financial implications

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