



**Australian Government**

**Department of Health**

# **MSAC Application 1647**

## **Brexucabtagene autoleucel for relapsed or refractory mantle 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](mailto:hta@health.gov.au)

Website: [www.msac.gov.au](http://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 lobbyist acting on behalf of an Applicant?

Yes

No

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

Not applicable

## PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

### 3. Application title

Brexucabtagene autoleucl for the treatment of patients with mantle cell lymphoma that has relapsed following, or is refractory, to treatment with: an anthracycline- or bendamustine-containing chemotherapy; an anti-CD20 antibody; and a Bruton’s tyrosine kinase (BTK) inhibitor (e.g., ibrutinib).

### 4. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

Mantle cell lymphoma (MCL) is an aggressive subtype of non-Hodgkin lymphoma (NHL) with distinctive clinical, biological, and molecular characteristics (Fakhri 2017)<sup>1</sup>. Frontline therapies for MCL can lead to high objective response rates (ORRs) and complete response (CR) rates of up to 53% (Flinn 2014<sup>2</sup>, Kluijn-Nelemans 2012<sup>3</sup>, Lenz 2005<sup>4</sup>, Robak 2015<sup>5</sup>). Despite high ORRs for frontline therapy, treatment is not considered curative and most patients experience relapse (Martin 2016<sup>6</sup>). Relapse is typically treated with a BTK inhibitor treatment however, again, most patients’ experience progression following such treatment. Patients experiencing disease progression after a BTK inhibitor have limited treatment options. Outcomes following salvage therapy are poor with ORRs ranging from 20% to 42%, median duration of response (DOR) ranging from 3 to 5.8 months, and median overall survival ranging from 2.5 to 9 months (Cheah 2015<sup>7</sup>, Epperla 2017<sup>8</sup>, Jain 2018a<sup>9</sup>, Martin 2016<sup>6</sup>, Wang 2017<sup>10</sup>).

### 5. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

Brexucabtagene autoleucl 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 then expanded to several million and the modified cells are then infused back into the patient, where they target and kill cancer cells.

REDACTED.

### 6. (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?

Not applicable

### (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:

Not applicable

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

Not applicable

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

Not applicable

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

- Yes  
 No

**(g) If yes, please advise:**

Funding of brexucabtagene autoleucl through the same block funding mechanism that has been agreed by the Commonwealth and the States that is currently used to fund other CAR T-cell therapies **REDACTED** is sought.

**7. What is the type of service:**

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

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

- i.  To be used as a screening tool in asymptomatic populations  
ii.  Assists in establishing a diagnosis in symptomatic patients  
iii.  Provides information about prognosis  
iv.  Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy  
v.  Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

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

- Pharmaceutical / Biological  
 Prosthesis or device  
 No

**10. (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 may be administered to some patients in the period between the collection of cells and the infusion of brexucabtagene autoleucl. Bridging therapy may be required in patients who have a high disease burden to ensure that the patient remains viable to have the brexucabtagene autoleucl product infused. The most commonly administered bridging therapies administered in the key study were dexamethasone and ibrutinib, both of which are PBS-listed for patients with MCL.

Conditioning chemotherapy is required to be administered prior to infusion of brexucabtagene autoleucl. The lymphodepleting chemotherapy regimen administered in the key ZUMA-2 study consisted of: fludarabine 30 mg/m<sup>2</sup> intravenous (IV) and cyclophosphamide 500 mg/m<sup>2</sup> IV, each administered on the fifth, fourth and third day prior to infusion of brexucabtagene autoleucl. Both of these therapies are available as unrestricted benefits on the PBS.

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

**REDACTED.**

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

Dexamethasone: 1292B, 2507Y, 1291Y, 2509C, 3472R  
Ibrutinib: 11419B  
Fludarabine: 4393F  
Cyclophosphamide: 4327R  
Tocilizumab: not reimbursed for the CRS indication  
REDACTED

**(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?**

Not applicable

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

Not applicable

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

Not applicable

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

Not applicable

**(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?**

Not applicable

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

Not applicable

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

There are a number of stages in the process of delivering brexucabtagene autoleucel that require the use of consumables e.g., collection of leucocytes from the patient by leukapheresis; administration of bridging therapy, administration of conditioning chemotherapy, infusion of brexucabtagene autoleucel.

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

13. (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following 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) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

- Class III  
 AIMD  
 N/A

14. (a) 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 no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

- Yes (if yes, please provide details below)  
 No

15. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?

REDACTED

16. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?

REDACTED

## PART 4 – SUMMARY OF EVIDENCE

17. Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
1	Phase II multicentre, open-label, non-comparative study	ZUMA-2 study NCT02601313  Wang M et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. <i>N Engl J Med</i> 2020;382(14):1331-1342. DOI: 10.1056/NEJMoa1914347	Evaluation of the efficacy of brexucabtagene autoleucl in 60 patients and safety in 68 patients with relapsed or refractory MCL.  Brexucabtagene autoleucl induced durable remissions in a majority of patients with relapsed or refractory mantle-cell lymphoma. The adverse event profile of brexucabtagene autoleucl is consistent with that reported with other CAR T-cell therapies.	<a href="https://www.nejm.org/doi/full/10.1056/NEJMoa1914347">https://www.nejm.org/doi/full/10.1056/NEJMoa1914347</a> [Last accessed: 26 Jun 2020]	2020

\* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

\*\* Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.

\*\*\* If the publication is a follow-up to an initial publication, please advise.

18. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

Not applicable

## PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

19. List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):

REDACTED

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

REDACTED

21. List the consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):

REDACTED

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

Novartis Pharmaceuticals Australia Pty Ltd produce tisagenlecleucel.

Gilead Sciences Pty Limited (same sponsor) produce axicabtagene ciloleucel.

23. Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):

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

*Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.*



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

## ***PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION***

### **24. 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:**

#### Mantle cell lymphoma

MCL is an aggressive subtype of NHL with distinctive clinical, biological, and molecular characteristics (Fakhri 2017<sup>1</sup>). The molecular hallmark of MCL is the chromosomal translocation t(11;14)(q13;q32), which results in an overexpression of cyclin D1 (a protein that stimulates cell growth) (Schieber 2018<sup>11</sup>). This overexpression leads to an abnormal growth of B-cells, which make antibodies to fight infection.

Typically, MCL appears as lymphadenopathy however, there can be frequent manifestation of disease in extranodal sites (bone marrow, gastrointestinal, spleen, liver, blood, etc.) (Schieber 2018<sup>11</sup>, Argatoff 1997<sup>12</sup>, Cheah 2016<sup>13</sup>). As a result, dependent on the sites involved, symptoms can vary. Typical symptoms include: loss of appetite and weight loss; fever; night sweats; nausea and/or vomiting; indigestion, abdominal pain or bloating; a feeling of “fullness” or discomfort as a result of enlarged tonsils, liver or spleen; pressure or pain in the lower back that often extends down one or both legs; or fatigue from anaemia (Leukemia & Lymphoma Society 2018<sup>14</sup>).

Prognosis of patients newly diagnosed with MCL is variable. The simplified MCL International Prognostic Index (s-MIPI, shown in **Table 1**) uses four independent factors (age, Eastern Cooperative Oncology Group [ECOG] performance status, blood lactate dehydrogenase, and leukocyte count) to stratify patients into low-, intermediate-, and high-risk prognostic groups (Hoster 2008<sup>15</sup>). The s-MIPI assigns a score based on each of these factors to each patient, corresponding to a prognostic risk group:

- Score of 0-3 => low risk
- Score of 4-5 => intermediate risk
- Score of > 5 => high risk

**Table 1: Simplified MCL Lymphoma Prognostic Index (sMIPI)**

Points	Age (years)	ECOG-PS	LDH (vs ULN)	WBC (x 10 <sup>9</sup> /L)
0	< 50	0 - 1	< 0.67	< 6.700
1	50 - 59	-	0.67 – 0.99	6.700 – 9.999
2	60 – 69	2 - 4	1.000 – 1.49	1.000 – 14.999
3	≥ 70	-	≥ 1.5000	≥ 15.000

Abbreviations: ECOG-PS = Eastern Cooperative Oncology Group Performance Status; LDH = lactic acid dehydrogenase in IU/L; ULN = upper limit of normal in IU/L (normal range is between 140 and 280 IU/L; WBC = white blood cell count

An additional independent prognostic factor is the Ki-67 index, which measures tumour cell proliferation. A Ki-67 ≥ 30% was found to be strongly adversely prognostic. A modified MIPI incorporating the Ki-67 as well as the standard MIPI elements demonstrated improved discriminatory power when estimating progression-free survival (PFS) based on risk group (Hoster 2016<sup>16</sup>).

Staging defines disease location and extent, and also suggests additional prognostic information (Cheson 2014<sup>17</sup>). The various stages are illustrated in **Figure 1**. Typically, patients are diagnosed with Stage III or IV disease (NCCN Guidelines, 2020<sup>18</sup>, Smith 2015<sup>19</sup>).

#### **Figure 1: Diagrammatic representation of the stages of mantle cell lymphoma**

**REDACTED**

## Epidemiology of MCL

The age-standardised incidence of MCL in Australia was reported to be 0.5 per 100,000 person-years in the period from 1997 to 2006, increasing, on average, by 4.2% (95% CI: 0.5% - 8.1%) per annum (van Leeuwen 2014<sup>20</sup>). The increasing incidence likely reflects its recognition as a distinct condition and improved diagnostic specificity with the introduction of immunohistochemical staining for cyclin D1. The condition is associated with male predominance, with the ratio of incidence being 2-4:1 for males versus females (van Leeuwen 2014<sup>20</sup>). The incidence of MCL increases with increasing age, with the median age of diagnosis estimated at 68 years (Zhou 2008<sup>21</sup>).

- 25. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:**

REDACTED

The diagnosis of MCL is made based on assessment of tissue collected by biopsy. MCL is characterised by overproduction of the cyclin D1 protein, which is identified via immunohistochemistry. Cytogenetic detection of the t(11;14) translocation that gives rise to the overproduction of cyclin D1 may be identified via either karyotyping or fluorescence in situ hybridisation (FISH).

- 26. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):**

**Figure 2** provides a flow chart depicting the clinical management pathway leading up to the point where brexucabtagene autoleucl would become a treatment option.

### Frontline treatment

As discussed at 24. above, MCL has a variable course however, in the majority of patients, MCL is associated with an aggressive clinical course.

In patients who are eligible (typically younger, fitter patients), administration of intensive chemotherapy followed by consolidation with autologous stem cell transplant (ASCT) is the treatment of choice (Tang & Kuruvilla<sup>22</sup>, 2018, Fakri 2017<sup>1</sup>). Given the median age at diagnosis is 68 years, the population eligible for such intensive therapy is limited. When high intensity induction and ASCT cannot be used, less toxic treatment strategies are employed. Typically, a bendamustine-based chemotherapy regimen that includes an anti-CD20 monoclonal antibody therapy will be administered.

Outcomes following frontline therapy are variable. High response rates and high rates of long term survival have been observed in some patients (Geisler 2012<sup>23</sup>, Fakri 2017<sup>1</sup>).

### Treatment of relapsed/refractory MCL

Refractory and relapsed MCL is typically treated with either allogeneic stem cell transplant or a BTK inhibitor treatment ( $\pm$  allogeneic stem cell transplant). Although efficacy of BTK inhibitors in this setting has been observed, most patients experience progression following such treatment due to primary or acquired resistance to treatment (Martin 2016<sup>6</sup>).

### Treatment of patients who are refractory to or have relapsed following treatment with BTK inhibitors for relapsed/refractory MCL

Limited treatment options are available for patients who relapse or are refractory to treatment with BTK inhibitors. Salvage chemotherapy is typically used in patients who are fit enough to tolerate such treatment. In this setting, MCL is rapidly fatal. Outcomes following salvage therapy are poor with median overall survival ranging from 5.8 to 10 months (Cheah 2015<sup>7</sup>, Jain 2018<sup>9</sup>, Martin 2016<sup>6</sup>).

**Figure 2: Management algorithm for MCL in Australia, showing proposed positioning of brexucabtagene autoleucl**

REDACTED

**PART 6b – INFORMATION ABOUT THE INTERVENTION**

**27. Describe the key components and clinical steps involved in delivering the proposed medical service:**

Brexucabtagene autoleucl is a CAR T-cell product that is unique to each patient. Each individual 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 then expanded to several million and the modified cells are then infused back into the patient. The steps involved in developing and eventually delivering the product are illustrated in **Figure 3** and are described in greater detail:

1. Leukapheresis and harvesting of peripheral blood mononuclear cells: a sufficient amount of blood is drawn from patients to obtain enough peripheral blood mononeuclear cells to support the manufacture of engineered T-cells. The remaining blood products are transfused back into the patient. REDACTED
2. Isolation of T-cells: In the laboratory, T-cells are purified from the peripheral blood cells that were collected from patients. REDACTED
3. Modification of T-cells: The T-cells are then genetically modified REDACTED.
4. Expansion of CAR T-cells: Following modification, the T-cells are then cultured in the laboratory. REDACTED.
5. Testing and shipping of CAR T-cells: REDACTED.
6. Bridging therapy (if necessary): Patients are monitored while the production of CAR T-cells is in progress. If necessary, patients may receive bridging therapy (typically consisting of dexamethasone or a BTK inhibitor) to ensure the patient remains viable for infusion of brexucabtagene autoleucl.
7. Conditioning chemotherapy: Prior to infusion of brexucabtagene autoleucl, 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<sup>2</sup>/day) plus cyclophosphamide (500 mg/m<sup>2</sup>/day) for three days (on the fifth, fourth, and third day before the infusion of brexucabtagene autoleucl on Day 0).
8. Infusion of brexucabtagene autoleucl: Brexucabtagene autoleucl is a single infusion product. Each bag for IV infusion contains a suspension of anti-CD19 CAR T-cells. REDACTED

**Figure 3: Steps in the manufacture and delivery of brexucabtagene autoleucl**

REDACTED

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

REDACTED

**29. 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?**

Not applicable

**30. 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):**

REDACTED

**31. If applicable, identify any healthcare resources or other medical services that would need to be delivered at the same time 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 brexucabtagene autoleucl. Bridging therapy may be required in patients who have a high disease burden to ensure that the patient remains viable to have the brexucabtagene autoleucl product infused. The most commonly administered bridging therapies administered in the key study were dexamethasone and ibrutinib, both of which are PBS-listed for patients with MCL.

Conditioning chemotherapy is required to be administered in the days prior to infusion of brexucabtagene autoleucl.

Paracetamol 500 mg to 1,000 mg and diphenhydramine 12.5 to 25 mg were administered one hour prior to infusion in the key ZUMA-2 trial.

**REDACTED**

Administration of brexucabtagene autoleucl is performed under the supervision of a haematologist or haematologist-oncologist.

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

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

Haematologists and haematologist-oncologists

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

Not applicable

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

As with the other CAR T-cell therapies, it is proposed that brexucabtagene autoleucl will only be able to be administered in accredited treatment centres. **REDACTED**

**35. 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:**

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

**36. (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:**

**REDACTED**

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

**REDACTED**

**PART 6c – INFORMATION ABOUT THE COMPARATOR(S)**

- 38. 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 (including identifying health care resources that are needed to be delivered at the same time as the comparator service):**

The main comparator for brexucabtagene autoleucl is expected to be salvage chemoimmunotherapy given that it is the therapy most likely to be displaced by brexucabtagene autoleucl.

REDACTED.

- 39. 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

- 40. Define and summarise the current clinical management pathway/s that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards, including health care resources):**

Patients being treated with salvage therapies have exhausted all known effective treatment options. Following salvage chemotherapy, patients are likely to be managed with best supportive care (BSC), further salvage therapy or they may be enrolled in a clinical trial of a therapy under investigation.

- 41. (a) Will the proposed medical service 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)

- (b) If instead of (i.e. alternative service), please outline the extent to which the current service/comparator is expected to be substituted:**

It is likely that brexucabtagene autoleucl will substitute for salvage therapies in the vast majority of patients who have received treatment with a BTK inhibitor.

- 42. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service, including variation in health care resources (Refer to Question 39 as baseline):**

Availability of brexucabtagene autoleucl for patients with progression of disease after treatment with a BTK inhibitor would likely become the standard of care in such patients. The use of BSC, including use of largely ineffective salvage therapies, would be used in the last line management of patients.

**PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME**

- 43. 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):**

Brexucabtagene autoleucl is superior in terms of effectiveness to use of salvage therapy in adult patients ( $\geq 18$  years of age) with relapsed or refractory MCL following treatment with, or demonstrating intolerance of treatment with, a BTK inhibitor. Brexucabtagene autoleucl induced durable remissions in a majority of patients with relapsed or refractory MCL in the post BTK inhibitor setting.

The therapy is associated with adverse effects that are consistent with those reported with other CAR T-cell therapies.

- 44. Please advise if the overall clinical claim is for:**

- Superiority  
 Non-inferiority

**45. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:**

**Safety Outcomes:**

- 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)

**Clinical Effectiveness Outcomes:**

- Objective response rate (ORR) and complete response rate (CRR)
- Duration of response
- Health-related quality of life (HRQoL) in patients achieving and those not achieving response
- Survival in responders and non-responders
- Quality of life in responders and non-responders
- Progression-free survival (PFS)
- HRQoL in patients who are progression-free and those with progression
- Overall survival
- Quality adjusted survival

**Other outcomes:**

- Percentage of patients having brexucabtagene autoleucl infused of those who underwent leukapheresis
- Time from collection (leukapheresis) to infusion of brexucabtagene autoleucl
- 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

**46. Estimate the prevalence and/or incidence of the proposed population:**

The age-standardised incidence of MCL in Australia was reported to be 0.5 per 100,000 person-years in the period from 1997 to 2006, increasing, on average, by 4.2% (95% CI: 0.5% - 8.1%) per annum (van Leeuwen 2014).

REDACTED

**47. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:**

The proposed therapy involves the administration of a single infusion.

**48. How many years would the proposed medical service(s) be required for the patient?**

The proposed therapy involves the administration of a single infusion.

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

REDACTED

**50. Estimate the anticipated uptake of the proposed medical service 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:**

REDACTED

## PART 8 – COST INFORMATION

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

REDACTED

52. Specify how long the proposed medical service typically takes to perform:

REDACTED

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

Not applicable

## PROPOSED PICO CRITERIA

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

REDACTED

**Table 2: Summary of proposed PICO criteria**

Component	Description
Population	REDACTED
Intervention	Brexucabtagene autoleucl
Comparator	Salvage chemotherapy
Outcomes	<p><u>Clinical Effectiveness:</u></p> <ul style="list-style-type: none"> <li>Objective response rate (ORR) and Complete response rate (CRR)</li> <li>Duration of response</li> <li>Health-related quality of life (HRQoL) in patients achieving and those not achieving response</li> <li>Survival in responders and non-responders</li> <li>Quality of life in responders and non-responders</li> <li>Progression-free survival (PFS)</li> <li>HRQoL in patients who are progression-free and those with progression</li> <li>Overall survival</li> <li>Quality adjusted survival</li> </ul> <p><u>Clinical efficacy:</u></p> <ul style="list-style-type: none"> <li>Percentage of patients having brexucabtagene autoleucl infused of those who underwent leukapheresis</li> <li>Time from collection (leukapheresis) to infusion of brexucabtagene autoleucl</li> </ul> <p><u>Safety Outcomes:</u></p> <ul style="list-style-type: none"> <li>Incidence of adverse events (AEs) and serious adverse events (SAEs)</li> <li>Incidence of events of special interest (e.g., cytokine release syndrome)</li> </ul> <p><u>Cost-effectiveness:</u></p> <ul style="list-style-type: none"> <li>Healthcare resource use and associated costs (including pre- and post-infusion), presented in disaggregated and aggregated format</li> <li>Incremental cost per life year gained (LYG)</li> <li>Incremental cost per quality adjusted life year (QALY)</li> </ul> <p><u>Financial implications:</u></p> <ul style="list-style-type: none"> <li>Number of patients suitable for treatment</li> <li>Number of patients who receive treatment and associated financial implications</li> </ul>



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