Population

Describe the population in which the proposed health technology is intended to be used:
Multiple myeloma (MM) is a cytogenetically heterogeneous clonal plasma cell proliferative disorder characterised by an abnormal serum and/or urine immunoglobulin (known as M protein). As MM progresses and patients relapse following initial treatment, the presence of sub-clonal populations of malignant plasma cells becomes increasingly prevalent. Typical clinical features include bone disease (and bone loss) with skeletal pain, impaired renal function, anaemia, fatigue, hypercalcaemia, recurrent and/or persistent bacterial infection, and/or hyperviscosity of the blood (Quach et al 2022). Together, these symptoms are associated with significant morbidity and can result in death in patients who are unable to receive or no longer responsive to available therapies.

MM follows a relapsing and remitting course as patients receive multiple lines of therapy. Although current standard treatments for MM may result in remission, most patients will relapse as there is no cure for the disease. The duration of response and remission typically gets shorter with each line of therapy, and is the result of plasma cell clonal evolution, acquiring mutations that can confer high risk features and resistance to standard therapy. Furthermore, there is significant patient attrition at each line, as patients become unsuitable for further therapy and succumb to the disease (Zhao, Wellard et al. 2019).

This application focuses on late-stage MM, in particular fifth-line plus (5L+) MM, after a person's myeloma has been treated with at least four prior lines of therapies (including an immunomodulatory drug [IMiD], proteosome inhibitor [PI] and anti-CD38 monoclonal antibody). Compared with the number of patients diagnosed and receiving first-line (1L) treatment for MM, the number of patients reaching the 5L+ MM setting is small and is the result of significant rates of attrition at each line of therapy as patients become unsuitable for further therapy and succumb to the disease (Zhao, Wellard et al. 2019). In the previous application for ciltacabtagene autoleucel (cilta-cel) was for patients with fourth-line plus (4L+) MM after a PI, IMiD and anti-CD38. Patients with 5L+ relapsed or refractory MM (RRMM) have even fewer treatment options than people with 4L+ RRMM as they have exhausted and become refractory to even more therapies, and thus the clinical need is further amplified.

Several medicines are listed on the PBS for the 5L+ MM treatment setting because of their line agnostic RRMM PBS restrictions including pomalidomide, carfilzomib, lenalidomide, bortezomib, selinexor, elotuzumab and thalidomide. However, many patients are refractory to these treatments by this stage of the disease and thus have exhausted these options, and if re-treated are unable to induce a meaningful response to therapy. This highlights the substantial unmet need for the later line MM population who have very limited treatment options. Thus, despite medicines being available for prescription, there is a significant lack of effective treatment options for this population. By the time patients reach 5L therapy they have previously been treated with most of these therapies, or these classes of medicine. Further, as the duration of response and remission typically gets shorter with each line of therapy, the benefits of currently available therapies in the 5L+ MM setting are very limited. This is seen by short durations of progression-free survival (PFS) and a poor survival prognosis as supported by multiple data sources, including clinical trials and real-world evidence (which will be submitted as key evidence within ADAR).

Janssen is requesting funding for the 5L+ MM including a PI, IMiD and anti-CD38, to address the issues raised by the MSAC and the States/Territories in July 2022 (MSAC ID 1690). This positioning intends to facilitate timely access to cilta-cel for a population with a high clinical need while reducing the overall costs of cilta-cel to Government and implementation challenges highlighted by the States.

[redacted]

Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed health technology, describing 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 technology:

Referral for cilta-cel

Patients will be monitored by their haematologists throughout MM treatment to determine remission and relapse status (determined using objective measurement of response, as per the PBAC rules for continuation and cessation. If patients reach the fifth line setting, they may be assessed for eligibility for cilta-cel and referred to a treating public hospital by their haematologist or haematological oncologist. Further, patient selection and referral decisions will be determined by a multi-disciplinary team (MDT). Additional information will be provided within the ADAR.

Provide a rationale for the specifics of the eligible population:

The previous application for ciltacabtagene autoleucel (cilta-cel) was for patients with 4L+ MM after a PI, IMiD and anti-CD38. Patients with 5L+ RRMM have even fewer treatment options than people with 4L+ RRMM as they have exhausted and become refractory to even more therapies, and thus the clinical need is further amplified. Janssen is requesting funding for the 5L+ MM including a PI, IMiD and anti-CD38, to address the issues raised by the MSAC and the States/Territories in July 2022 (MSAC ID 1690). This positioning intends to facilitate timely access to cilta-cel for a population with a high clinical need while reducing the overall costs of cilta-cel to Government and implementation challenges highlighted by the States.

Are there any prerequisite tests?

No

Are the prerequisite tests MBS funded?

N/A

Please provide details to fund the prerequisite tests:

N/A

Intervention

Name of the proposed health technology:

Ciltacabtagene autoleucel (cilta-cel)

Describe the key components and clinical steps involved in delivering the proposed health technology:

Cilta-cel is a B cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy. Cilta-cel is prepared from the patient's peripheral blood mononuclear cells,

which are obtained via a standard leukapheresis procedure. A replication incompetent lentiviral vector is used to introduce an anti-BCMA chimeric antigen receptor (CAR) gene into patient derived human T-cells.

Treatment with cilta-cel initially is likely to be limited to a small number of key specialist public hospital centres across the Australian states and territories. Several hospitals are currently trial centres for cilta-cel and three of these are also delivering Kymriah®, and thus would have relevant clinical experience and protocols for delivering this medical service. Further, cilta-cel will be prescribed and delivered by physicians experienced in the treatment of haematological malignancies (i.e., MM) in selected accredited treatment centres. There will be some form of accreditation of clinical sites and prescribers required to deliver cilta-cel.

Further, patient selection and referral decisions will be determined by institution, state and National Multi Disciplinary Teams (MDT) which will ensure suitable patients who can tolerate CAR-T therapy are identified and prioritised for treatment. This level of decision making and consideration by MDTs will lead to better patient selection and achievement of optimal patient outcomes aligned to those seen in CARTITUDE-1.

Consistent with other CAR-Ts considered by MSAC, it is proposed that the use of cilta-cel will be limited to one successful infusion per lifetime (a successful infusion is when the patient with RRMM has been infused with the optimal cilta-cel dosage as per the TGA recommend dose).

The steps involved and resources used at each step are similar for cilta-cel to previously approved CAR-Ts, and is consistent with the steps outlined in the previous application for cilta-cel (ID 1690). Further details will be presented within the ADAR.

Step 1 – Referral: Patient eligibility for CAR-T will be discussed at Standard Tumour Stream MDT meetings. After this a national CAR-T patient prioritisation meeting will occur with the MDT. These meetings may include CAR-T specialists, national treating and referring centre clinical representatives, CAR-T fellows, CART nurse consultants, research nurses, apheresis nurses, cell logistics project managers and the CAR-T program managers.

Step 2 – Apheresis: Once diagnosed as eligible and suitable for cilta-cel, the patients will undergo a standard apheresis process to collect white blood cells (WBC). Prior to this process, patients will typically undergo preparation for apheresis and confirm suitability. The T cells from apheresis will be collected for transduction and undergo expansion to manufacture cilta-cel. Two apheresis collections may be performed to attain this target and is typically performed over 1-2 days.

Step 3 – Bridging therapy: Most patients receive bridging therapy as per clinical indication to maintain disease stability during the period of production of cilta-cel. Following cell collection, a patient's status will be maintained until the cells are manufactured and delivered back to the treatment site by bridging therapy. The clinical goal of bridging therapy is to achieve disease control of the myeloma ahead of CAR-T infusion.

It is anticipated that on average around 2 cycles of bridging therapy will be required for each patient receiving cilta-cel based on local expert clinical advice. Relevant bridging therapies in Australia are anticipated to include pomalidomide plus dexamethasone, carfilzomib plus dexamethasone, bortezomib plus dexamethasone, selinexor, elotuzumab or dexamethasone monotherapy.

Step 4 – Manufacture of cilta-cel: The mononuclear cells are enriched for T-cells and genetically modified ex vivo by transduction with a replication incompetent lentiviral vector to express a chimeric antigen receptor (CAR) comprising an anti-BCMA targeting domain. The transduced anti-BCMA CAR T-cells are expanded in cell culture, washed, formulated into a suspension and cryopreserved. Once the CAR-T product is manufactured, it will undergo full QA release at Raritan in the United States and then cold chain transported directly to hospital in Australia.

Step 5 – Conditioning (lymphodepletion): Approximately 4 to 5 weeks after apheresis, after the completion of manufacture and quality testing of cilta-cel, the patients are subjected to a conditioning regimen of IV cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 at three daily doses. The conditioning regimen will lead to lymphodepletion and help promote cilta-cel cell expansion in the patients.

Step 6 – Cilta-cel infusion: Cilta-cel is a single infusion product. Cilta-cel will be administered 5 to 7 days in the after start of the conditioning regimen at a public hospital. Treatment will be prescribed and monitored by an experienced haematologist working in a multidisciplinary team specialising in the provision of CAR-T cell therapy and whom have undergone appropriate accreditation and training.

Pre-infusion medications are administered to all patients (30 to 60 minutes) prior to cilta-cel infusion which include antipyretics and an antihistamine. Further, before the infusion and during the recovery period, tocilizumab (for managing cytokine release syndrome [CRS]) and emergency equipment will need to be available for use if needed.

The patients will be evaluated for safety on the day of cilta-cel infusion in case the infusion needs to be delayed.

Step 7 – Monitoring after infusion: Following the infusion, there will be a period of monitoring required. Monitoring requirements for cilta-cel are not expected to be significantly different from any other CAR-T therapies, including those considered by MSAC (i.e. Kymriah® and Yescarta®).

The setting of post infusion care for cilta-cel can vary by patient, by site and by the experience and capacity of the treating clinician and team. As such, patients are managed in both the inpatient and outpatient settings, consistent with other CAR-Ts currently funded in Australia.

Some patients may require a short inpatient admission as a consequence of cytokine release syndrome (CRS) onset and CAR-T neurotoxicities. Typically these toxicities may take up to 7 days to onset. Tocilizumab or methylprednisolone may be administered via IV infusion for the management of CRS or ICANS.

Step 8 – Long term patient assessment: Previous CAR-T therapies recommended by MSAC have required assessment of long-term patient outcomes. Consistent with the initial ADAR, Janssen will propose that a payment for outcome model for cilta-cel is linked to the achievement of response at a specified time point post infusion. Furthermore, Janssen is aware that data on the use of CAR-T therapies in Australia is currently recorded by the Australian Bone Marrow Transplant Recipient Registry (ABMTRR), with the cost of data collection met by the sponsor.

Identify how the proposed technology achieves the intended patient outcomes:
Intended patient outcomes are achieved through the superior efficacy of cilta-cel over current standard of care treats in the 5L+ RRMM setting, whilst having a manageable safety profile.

The clinical efficacy and safety of cilta-cel was investigated in the single arm CARTITUDE-1 study in patients with RRMM after 3 prior therapies including a PI, IMiD and an anti-CD38. Cilta-cel was studied in a population which is reflective of the requested population for funding in Australian clinical practice (via this application), with [redacted] of the CARTITUDE-1 population reflecting a 5L+ RRMM population, and [redacted] of the 5L+ CARTITUDE-1 population were refractory to an PI, IMiD and anti-CD38 (including [redacted] exposure to these classes of medicines).

The CARTITUDE-1 close-out data cut has now reported after a median duration of follow-up of 33.4 months (October 2022 database lock). As CARTITUDE-1 is a single arm study, indirect comparisons will be submitted in the ADAR for the assessment of comparative efficacy and safety versus the relevant comparator studies. Several comparator studies are available that reflect the requested population and standard of care in Australia across a variety of trial and real world cohorts. Treatment with cilta-cel resulted in a highly effective and clinically meaningful response in patients with RRMM as follows:

Superior PFS - Cilta-cel was demonstrated to be statistically superior over every comparator study for the outcome of PFS. In CARTITUDE-1, the median PFS for the ITT 5L+ population and mITT 5L+ population was [redacted]months (95% CI [redacted], [redacted]) and [redacted]months (95% CI [redacted], [redacted]), respectively. This represents a [redacted] to [redacted]fold improvement over current 5L+ RRMM therapies where median PFS ranges from 2.6 months to 6.2 months.

Superior OS - Median OS in CARTITUDE-1 was not reached even after a median follow-up of [redacted] months ((ITT 5L+ population NE [95% CI, [redacted], [redacted]]). In contrast, the median OS in the majority of comparator studies of current 5L+ RRMM therapies was <12 months.

Superior ORR and CR or better rates - The ability of cilta-cel to induce an overall response, and importantly a deep response (i.e., ≥CR), was superior to current 5L+ RRMM therapies. Overall, the responses elicited by cilta-cel were prompt (median time to best response of [redacted]months), deep ([redacted]and [redacted]% of patients in the ITT 5L+ and mITT 5L+ population, respectively achieved CR or better) and durable (median duration of response of [redacted]months (95% CI: [redacted], [redacted])), and thus represents unprecedented improvements in outcomes in a heavily pre-treated MM population who typically respond very poorly to treatment ([redacted]% achieve CR or better).

Superior TTNT- Median TTNT in CARTITUDE-1 was [redacted]months (95% CI: [redacted], [redacted]) and [redacted]months (95% CI: [redacted], [redacted]) in the ITT/all-enrolled 5L+ and mITT/all-treated population, respectively. The median TTNT achieved with cilta-cel represents [redacted] to [redacted]-fold improvement over the median TTNT achieved with current 5L+ therapies, where median TTNT ranged from 3.3 to 5.6 months.

Improved HRQoL - patients participating in HRQoL evaluations in CARTITUDE-1 reported improvement in EQ-5D-5L VAS and EORTC QLQ-C30 GHS outcomes over time and these improvements remained consistently and significantly higher for CARTITUDE-1 5L+ patients than LocoMMotion 5L+ patients from Day 0 to 520.

Manageable safety profile - CARTITUDE-1 also demonstrated that cilta-cel has a manageable safety profile. There was no difference in most safety outcomes between the September 2020 data cut submitted in the initial ADAR (median follow-up of 12.4 months) and the October 2022 database lock (median follow-up of 33.4 months), after an additional 21 months of follow-up. The proportion of patients reporting Treatment Emergent Adverse Events (TEAEs), serious TEAEs, and TEAEs having an outcome of death in the all-treated population was the same across the two timepoints, indicating that the frequency, type, and severity of TEAEs remained stable over time with minimal new onset AEs. This supports the benefit of one-off treatment with cilta-cel and a prolonged treatment-free interval whereby adverse events are likely to be limited to the early post-treatment phase.
Overall, the AEs observed in CARTITUDE-1 are considered manageable and consistent with the safety profile of CAR-T therapy. Adverse events may occur during the initial post-treatment period as opposed to an ongoing and cumulative basis as with current 5L+ RRMM therapies.

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?
Yes

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:
Cilta-cel (CARVYKTI®) was registered on the Australian Register of Therapeutic Goods (ARTG) on the 6th June 2023. Cilta-cel was registered on the ARTG as a Class 4 biological ('Cellular Therapies - T cells-Ciltacabtagene autoleucel, cryopreserved-T-CARVYKTI - Janssen-Cilag Pty Ltd - Injection, intravenous infusion – Bag and the AUST R 410143').

Cilta-cel consists of autologous CAR-T cells designed to target the biomarker, B cell maturation antigen (BCMA) which is a type III membrane protein and a part of the tumour necrosis receptor superfamily. BCMA is stably expressed in malignant multiple myeloma plasma cells in almost all patients with MM. Expression of BCMA in non-malignant cells is minimal and limited to plasma cells and a small subset of B cells. BCMA also facilitates MM plasma cell survival. This BCMA target distinguishes it from other CAR-T products currently approved by MSAC (Yescarta® and Kymriah® which target CD-19 in lymphomas).

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):
Yes

Provide details and explain:
The following limitations are applied to the proposed medical service:

Dosing: Cilta-cel is to be administered as a single dose for infusion per patient containing a suspension of chimeric antigen receptor (CAR)-positive viable T-cells. The dose is $0.5\text{-}1.0\times10^6$ CAR-positive viable T-cells per kg of body weight, with a maximum dose of 1×10^8 CAR-positive viable T-cells per single infusion. The infusion should be given 5 to 7 days after the start of the lymphodepleting regimen.

Number of CAR-T treatments in a lifetime: Consistent with other CAR-Ts considered by MSAC, it is proposed that the use of cilta-cel will be limited to one successful infusion per lifetime (a successful infusion is when the patient with RRMM has been infused with the optimal cilta-cel dosage as per the TGA recommend dose).

Prescriber: Cilta-cel will be prescribed and delivered by healthcare professionals experienced in the treatment of haematological malignancies (i.e., MM) in selected accredited treatment centres who are trained for administration and management of patients treated with cilta-cel.

Treatment centre: Treatment with cilta-cel initially is likely to be limited to a small number of key specialist public hospital centres across the Australian states and territories. Several hospitals are currently trial centres for cilta-cel and three of these are also delivering Kymriah®, and thus would have relevant clinical experience and protocols for delivering this medical service.

If applicable, advise which health professionals will be needed to provide the proposed health technology:
Infusion of cilta-cel will be delivered by a nurse and supervised by a haematologist in a hospital setting. This is consistent with the administration of the currently approved CAR-T therapies, Yescarta® and Kymriah®.

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:
It is not appropriate for this medical service to be delegated to another professional for delivery.

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:
Patient selection and referral decisions will be determined by institution, state and National Multi Disciplinary Teams (MDT) which will ensure suitable patients who can tolerate CAR-T therapy are identified and prioritised for treatment.

Patient eligibility for CAR-T will be discussed at Standard Tumour Stream multidisciplinary team (MDT) meetings. After this a national CAR-T patient prioritisation meeting will occur with the MDT. These meetings may include CAR-T specialists (including tumour stream leads), national treating and referring centre clinical representatives, CAR-T fellows, CART nurse consultants, research nurses, apheresis nurses, cell logistics project managers and the CAR-T program managers.

This level of decision making and consideration by MDTs, as well as appropriately defined eligibility criteria for cilta-cel under NHRA funding will lead to better patient selection and achievement of optimal patient outcomes aligned to those seen in CARTITUDE-1.

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?
Yes

Provide details and explain:

Accreditation

[redacted]

Training

[redacted]

Indicate the proposed setting(s) in which the proposed health technology will be delivered:

- ☐ Consulting rooms
- ☐ Day surgery centre
- ☐ Emergency Department
- ☐ Inpatient private hospital
- ☒ Inpatient public hospital
- ☐ Laboratory
- ☒ Outpatient clinic
- ☐ Patient's home
- ☐ Point of care testing
- ☐ Residential aged care facility
- ☐ Other (please specify)

[redacted]

Furthermore, it is Janssen's understanding that the NHRA includes funding from both the Commonwealth Government (50%) and the governments of the relevant states and territories (50%) (Addendum to the National Health Reform Agreement 2020-2025; NHRA-addendum-2020-2025.pdf (health.qld.gov.au). Thus, the same joint funding mechanism is requested for cilta-cel.

Is the proposed health technology intended to be entirely rendered inside Australia?

No

Please provide additional details on the proposed health technology to be rendered outside of Australia:

Most of the medical service will be rendered in Australia. The exception is the manufacturing of the cilta-cel CAR-T product which occurs in the Janssen manufacturing centre in Raritan (NJ, USA).

Comparator

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 nominated comparators that reflect Australian clinical practice are:

- Pomalidomide with dexamethasone (Pd),
- Carfilzomib with dexamethasone (Cd),
- Selinexor with dexamethasone (Sd).

List any existing MBS item numbers that are relevant for the nominated comparators:
N/A

Please provide a rationale for why this is a comparator:
In the initial ADAR lodged in February 2022 (ID1690), Pd, and Cd were identified as the most relevant comparators for 4L+ MM (i.e. including 5L+ MM). These were accepted by the MSAC and remain relevant comparators as part of this application and its ADAR. This application for 5L+ MM also includes the addition of Sd following its PBS listing for the 5L+ MM population in 2022. Clinical expert advice provided to Janssen has indicated that there is no standard of care in later line MM because the available options include ineffective regimens, and classes of therapies, previously received by this population for which their MM is refractory too. Thus, highlighting the lack of standard of care in this setting in Australia, a clear statement that new, and superior options, are desperately needed.

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator? (please select your response)

☐ None – used with the comparator
☐ Displaced – comparator will likely be used following the proposed technology in some patients
☒ Partial – in some cases, the proposed technology will replace the use of the comparator, but not in all cases
☐ Full – subjects who receive the proposed intervention will not receive the comparator

Please outline and explain the extent to which the current comparator is expected to be substituted:
Cilta-cel will not be used in 100% of the 5L+ MM population, and thus a patient may still be treated with Sd, Pd, or Cd, if they are not of suitable fitness for cilta-cel therapy. Despite the high efficacy shown in the CARTITUDE-1, not all patients in the 5L+ MM setting will be able to tolerate cilta-cel, so it will only partially replace and displace Sd, Pd, or Cd. Suitability and uptake of cilta-cel will be moderated by the fact that:

Only patients who have received prior PI, IMiD and anti-CD38 can receive cilta-cel. However, by the time a patient reaches 5L MM in Australian clinical practice it is highly likely they have had exposure to each of these treatment classes. Although daratumumab (anti-CD38 inhibitor) is only available on the PBS as a second-line option, it is also available compassionately, and has been since 2017, for people who have exhausted all PBS options and have not previously received prior anti-CD38 therapy (as described above).

Only a portion of patients will be able to tolerate or be fit enough for treatment and can travel to the treatment site which may be interstate. Receiving CAR-T therapy is a strenuous process needing apheresis, chemotherapy conditioning, and the infusion which is associated with a risk of significant toxicity. Thus, only those with sufficient fitness will be considered for it. This will inform the patient estimates presented in the ADAR relevant to this application.

Outcomes

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):

☒ Health benefits
☐ Health harms
☐ Resources
☐ Value of knowing

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:
N/A

Proposed MBS items

How is the technology/service funded at present? (for example: research funding; State-based funding; self-funded by patients; no funding or payments):
No funding (not currently funded)

Please provide at least one proposed item with their descriptor and associated costs, for each population/Intervention:
N/A – In accordance with CAR-Ts that have been evaluated by MSAC and are currently funded (i.e., Kymriah®) and treatment site survey results which confirm that the setting of care for cilta-cel will be the same as the current CAR-T's funded under the NHRA, Janssen understands that cilta-cel will not be funded through the MBS but through NHRA.

Proposed item details
N/A

Algorithms

Preparation for using the health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:

The management of patients with MM is individualised and many factors are considered in making treatment decisions determined by age, comorbidities, frailty, and disability.

Treatment of Newly diagnosed MM

At diagnosis, patients with MM are classified into transplant eligible and transplant ineligible. Eligibility for autologous transplantation is assessed on age, comorbidities and frailty. The upper age limit for transplantation is generally 70–75 years in Australia.

The treatment algorithm is informed by the Australian MSAG guidelines and the PBS restrictions for currently available therapies. Currently available myeloma therapies in Australia include four classes of therapeutic agents – proteosome inhibitors (PI [e.g. bortezomib, carfilzomib]), immunomodulator drugs (IMiDs [e.g. thalidomide, lenalidomide, pomalidomide]), monoclonal antibodies (elotuzumab, daratumumab) and most recently following the PBS listing of selinexor, selective inhibitor of nuclear export (SINE) (Quach et al 2019; Tomlinson et al, 2018).

Most transplant eligible patients will receive a bortezomib, lenalidomide plus dexamethasone (BLd) and go on to receive lenalidomide maintenance after transplantation. The MSAG clinical guideline (2022) recommends that patients who are ineligible for ASCT but who are fit or intermediate-fit should undergo standard treatment regimens containing an IMiD and/or a proteasome inhibitor (i.e., BLd, Ld or other bortezomib-based regimens [BCd]), while frail (and typically much older) patients should be considered for doublet therapies (i.e., Ld, Bd) with or without reduced dose-intensity.

Treatment of RR MM

The type of prior therapy received, response and associated toxicities with prior therapy are important factors which determine treatment of relapsed/refractory patients in the second line setting. Treatments PBS listed for patients with RRMM include lenalidomide, bortezomib, elotuzumab, carfilzomib, pomalidomide, selinexor and thalidomide. These treatments, may or may not be used in combination with chemotherapies and/or corticosteroids (most commonly dexamethasone). Lenalidomide, bortezomib, carfilzomib, elotuzumab, pomalidomide, selinexor and thalidomide have line agnostic PBS listings in the RRMM setting. Daratumumab, bortezomib and dexamethasone (DBd) is PBS listed for second-line MM only (i.e. not a line agnostic PBS listing).

No best sequence has been defined for RRMM but generally it is recommended to switch drug class at each relapse, especially if remission to prior medicines was short or a patient had concerning associated toxicity. Further, access and choice in the RRMM setting may also be determined by the PBS restrictions.

DBd is a clinically appropriate treatment option for most second line MM patients. DBd is also appropriate for patients who had previously received bortezomib-based therapy (unless patients are refractory, intolerant or contraindicated to bortezomib) or an IMiD, typically lenalidomide, as

1L treatment. Since DBd was PBS listed, its uptake has been very high (given its superior efficacy to other available therapies). As such, DBd is used at 2L in most patients.

The availability, and response to previous therapies received plays a major role in treatment selection in the later stage setting. Due to the PBS listings of BLd and Ld in the first-line and DBd in the second-line MM settings referred to above, it is anticipated that the use of lenalidomide will reduce in the 3L+ setting and that there will be an increase in the use of carfilzomib in the 3L setting as it is being displaced in the 2L setting by DBd. However, carfilzomib will also continue to be used in the 4L+ setting as a result of the PBS listings of pomalidomide, bortezomib and dexamethasone (PBd), and elotuzumab, lenalidomide and dexamethasone (ELd), which are likely to be used in the 3L setting for some patients. For 4L+ MM, pomalidomide and carfilzomib are generally prescribed in Australian clinical practice. Pomalidomide, is an IMiD, and is also PBS listed in combination with dexamethasone (i.e. without bortezomib) for patients who have failed treatment with both bortezomib and lenalidomide. Use of thalidomide in clinical practice is low across the MM pathway, and is diminishing, due to its toxicity, and thus is no longer reflected in the treatment algorithm.

The challenge with treating patients from 4L+ MM onwards, is that patients have generally exhausted most, if not all, classes of MM medicines, and thus have become refractory to these medicines. Selinexor was PBS listed for the 5L+ MM population in late 2022, and while this medicine does offer a new mechanism of action to those listed on the PBS, outcomes remain poor (i.e. median overall survival of 8.4 months in the 5L+ MM population). As PBS treatment options at the 5L+ setting of RR MM are extremely limited and response rates are low, clinicians are likely to explore other options for access to alternative medicines, such as clinical trial programs, compassionate use programs (including compassionate daratumumab) or private funding.

Is there any expectation that the clinical management algorithm *before* the health technology is used will change due to the introduction of the proposed health technology?
No

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:
N/A – no changes to clinical management algorithm

Use of the health technology

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:
Delivering cilta-cel involves apheresis, administration of bridging therapies and lymphodepleting conditioning regimen before infusion of the CAR-T cells. These are performed sequentially and not at the same time as each other (refer Intervention 'Describe the key components and clinical steps involved in delivering the proposed health technology' section for details of clinical steps).

Explain what other healthcare resources are used in conjunction with the comparator health technology:
Carfilzomib is administered by intravenous (IV) infusion in the hospital setting, while pomalidomide and selinexor are administered orally.

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:
As above. Cilta-cel requires healthcare resources for apheresis, bridging therapy, lymphodepletion and infusion. Carfilzomib requires healthcare resources for infusion, whilst selinexor and pomalidomide are orally administered.

Clinical management after the use of health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the proposed health technology:

Cilta-cel would both replace and displace comparator treatments. For some patients, after failure of cilta-cel, they will be treated with Cd, Pd or Sd (or alternative options via clinical trials, compassionate use programs etc). For others, based on the duration of response of cilta-cel, the high attrition rates between lines of therapy, and the general health of patients after a fourth line of treatment for MM, cilta-cel would be the patients' final line of treatment, and thus Cd, Pd, or Sd, would be replaced.

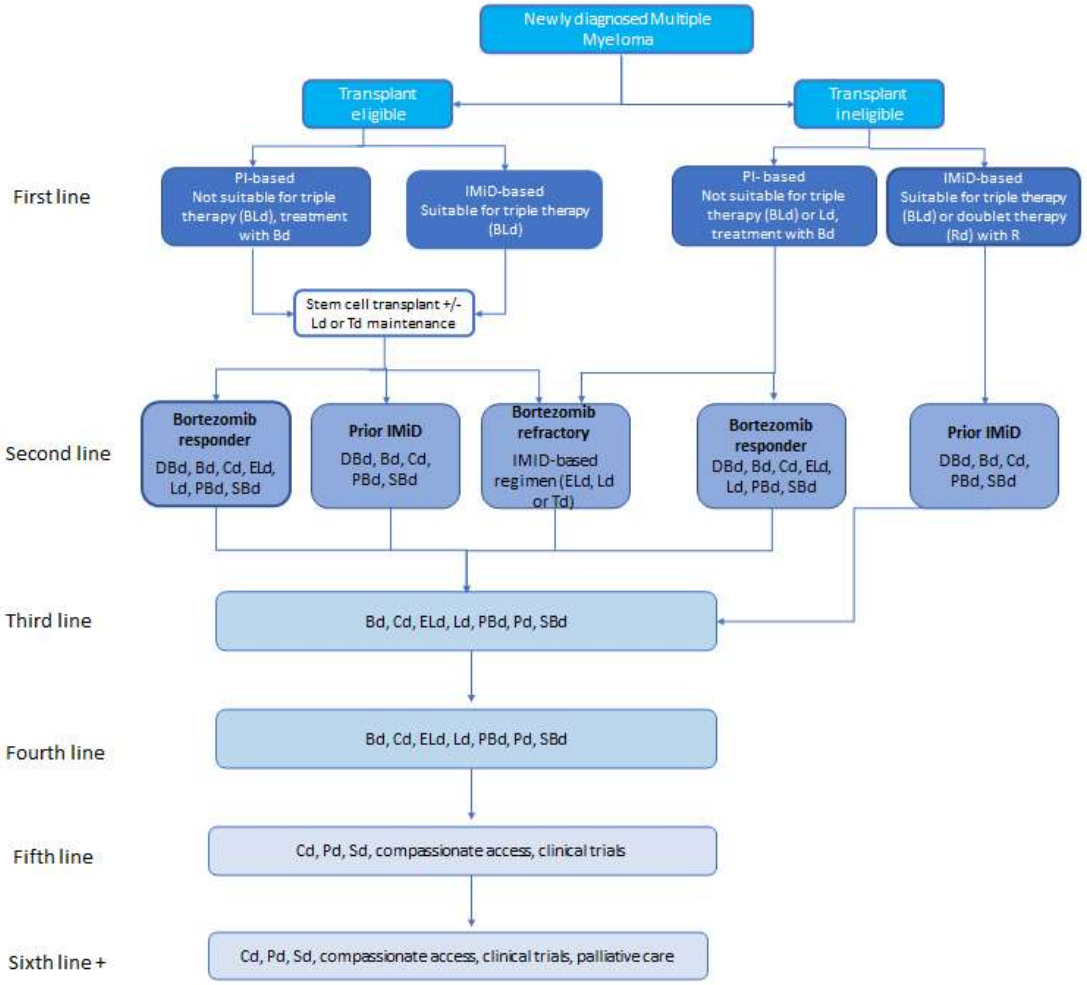
Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the comparator health technology:
The challenge with treating patients from 4L+ MM onwards, is that patients have generally exhausted most, if not all, classes of MM medicines, and thus have become refractory to these medicines, which explains the lack of standard of care and dismal outcomes reported in the MRDR analysis in these cohorts of patients (provided as evidence in the ADAR related to this application). As PBS treatment options at the 5L+ setting of RR MM are extremely limited and response rates are low, clinicians are likely to explore other options for access to alternative medicines, such as clinical trial programs, compassionate use programs or private funding.

Describe and explain any differences in the healthcare resources used *after* the proposed health technology vs. the comparator health technology:
Cilta-cel is a one-off procedure and thus patients with RRMM will no longer need to receive continuous therapy until progression. This results in improved quality of life relative to SoC therapies as there is no further treatment or consequences of ongoing treatment like AEs and repeat administration Furthermore, cilta-cel induces deep and meaningful responses which significantly extend life. Thus, patients can enjoy considerable periods of treatment free intervals, and for some patients, they will require no further treatment. Therefore cilta-cel addresses an area of high unmet medical need for Australian patients in which there are limited options and a poor prognosis.

Algorithms

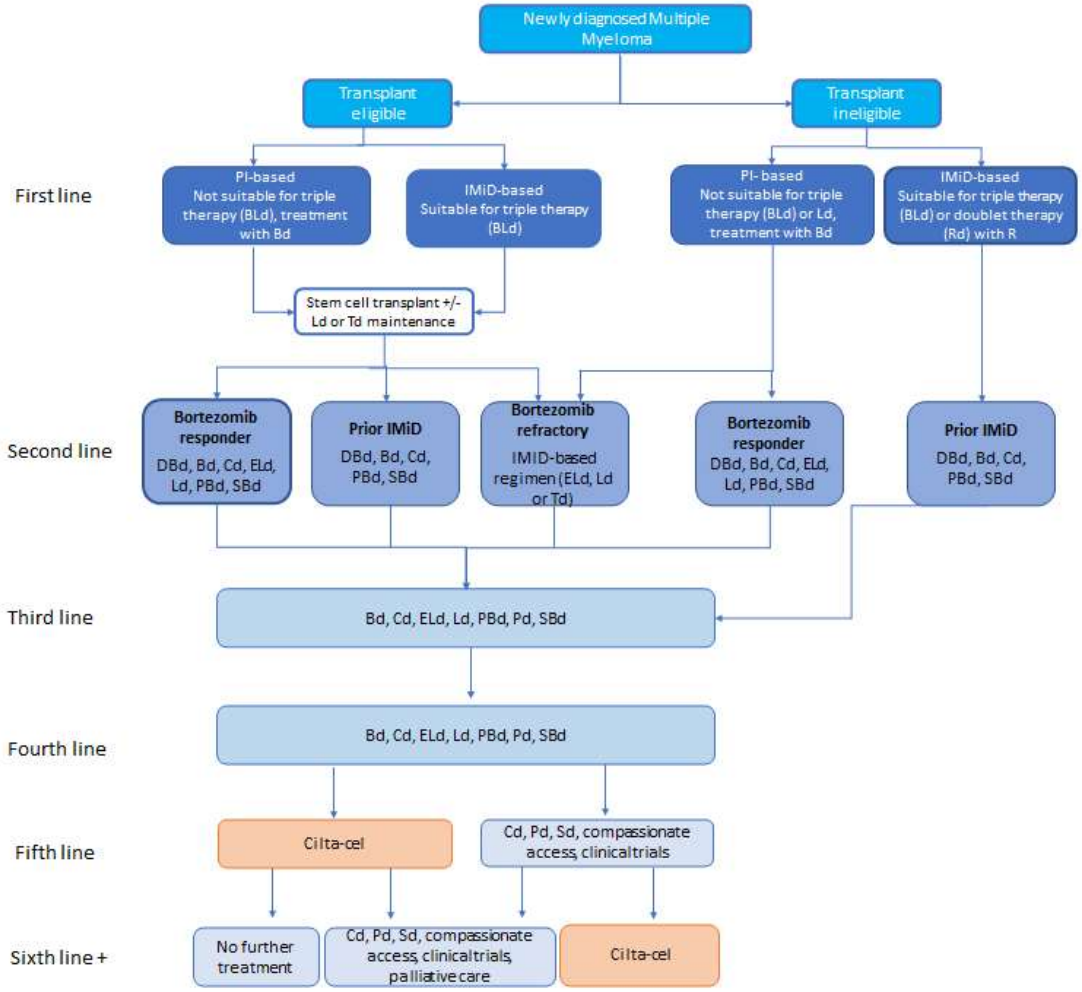
Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

Figure 1: Current clinical algorithm



Abbreviations: Proteasome inhibitor (PI); Immunomodulatory agent (ImiD); Selective inhibitor of nuclear export (SINE); Bd = bortezomib and dexamethasone; BLd = bortezomib, lenalidomide and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; ELd = elotuzumab, lenalidomide and dexamethasone; ImiDs = immunomodulator drugs; Ld = lenalidomide and dexamethasone; MM = multiple myeloma; PBd = pomalidomide, bortezomib and dexamethasone; Pd = pomalidomide and dexamethasone.

Figure 2: Proposed clinical algorithm



Abbreviations: Proteasome inhibitor (PI); Immunomodulatory agent (ImiD); Selective inhibitor of nuclear export (SINE); Bd = bortezomib and dexamethasone; BLd = bortezomib, lenalidomide and dexamethasone; Cd = carfilzomib and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; ELd = elotuzumab, lenalidomide and dexamethasone; ImiDs = immunomodulator drugs; Ld = lenalidomide and dexamethasone; MM = multiple myeloma; PBd = pomalidomide, bortezomib and dexamethasone; Pd = pomalidomide and dexamethasone.

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?

☒ Superior
☐ Non-inferior
☐ Inferior

Please state what the overall claim is, and provide a rationale:
The use of cilta-cel results in substantially superior health outcomes compared with current standard Australian practice in terms of response, progression-free survival (PFS) and overall survival (OS) in adult patients with RRMM who have received at least four prior lines of therapy (i.e., 5L+ MM), including a PI, IMiD and anti-CD38 antibody. Further, cilta-cel is associated with

different adverse events compared with current therapies, and a different profile in that the adverse events may occur during the initial period of therapy compared with an ongoing and cumulative basis with current therapies. This clinical claim is strongly supported by evidence, [redacted]

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?
N/A – cilta-cel is not an investigative technology

Identify how the proposed technology achieves the intended patient outcomes:
Please see response to this question under Intervention section 'Identify how the proposed technology achieves the intended patient outcomes' above.

For some people, compared with the comparator(s), does the test information result in:

A change in clinical management?
A change in health outcome?
Other benefits?

N/A – cilta-cel is not a test

Please provide a rationale, and information on other benefits if relevant:
N/A

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator?

☒ More costly
☐ Same cost
☐ Less costly

Provide a brief rationale for the claim:
Cilta-cel qualifies as a high cost, highly specialised therapy as per the definition under the NHRA (Addendum to the National Health Reform Agreement 2020-2025; NHRA-addendum-2020-2025.pdf (health.qld.gov.au)). The NHRA defines a high cost, highly specialised therapy as "TGA approved medicines and biologicals delivered in public hospitals where the therapy and its conditions of use are recommended by MSAC or PBAC; and the average annual treatment cost at the commencement of funding exceeds $200,000 per patient (including ancillary services) as determined by the MSAC or PBAC with input from the IHPA; and where the therapy is not otherwise funded through a Commonwealth program or the costs of the therapy would be appropriately funded through a component of an existing pricing classification."

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology.

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
PIVOTAL STUDY Phase Ib/II, Single arm, open label, multi-center study in patients with relapsed/refractory multiple myeloma (RRMM) (i.e., patients who received ≥3 prior lines of therapy (including PI, iMiD and anti-CD38 antibody) or double refractory to PI and iMiD).	CARTITUDE-1 Clinical trial identifier: NCT03548207 Martin T, Usmani SZ, Berdeja JG, Agha M, Cohen AD, Hari P, et al. Ciltacabtagene Autoleucel, an Anti-B-cell Maturation Antigen Chimeric Antigen Receptor T-Cell Therapy, for Relapsed/Refractory Multiple Myeloma: CARTITUDE-1 2-Year Follow-Up. J Clin Oncol. 2023;41(6):1265-74. Note: this publication is of an earlier data cut to that presented in the ADAR. Data in the ADAR is derived from an internal clinical study report of the close out data – see CARTITUDE-1 Janssen: Close-out analysis Clinical Study Report (CSR) below.	Evaluation of efficacy and safety of cilta-cel in patients with RR MM (n=19 in Phase 1b; n=68 in Phase 2). Primary endpoint: Phase 1b- incidence/severity of adverse events; Phase 2- overall response rate. Follow-up to publications included in first cilta-cel submission, data with median follow-up 28 months.	https://ascopubs.org/doi/10.1200/JCO.22.00842	4 June 2022 (online publication date)
	Cohen AD, Hari P, Htut M, Berdeja JG, Usmani SZ, Madduri D, et al. Patient Perceptions Regarding Ciltacabtagene Autoleucel Treatment: Qualitative Evidence From Interviews With Patients With Relapsed/Refractory Multiple Myeloma in the CARTITUDE-1 Study. Clin Lymphoma Myeloma Leuk. 2023;23(1):68-77.	Qualitative interviews were conducted in a subset of CARTITUDE-1 patients (n = 36) at screening, Day 100, and Day 184 post cilta-cel on living with MM, therapy expectations, and treatment experiences during the study. Follow-up to publications included in first cilta-cel submission.	https://www.clinical-lymphoma-myeloma-leukemia.com/article/S2152-2650(22)01692-5/fulltext	10 October 2022

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
	Martin T, Lin Y, Agha M, Cohen AD, Htut M, Stewart AK, et al. Health-related quality of life in patients given ciltacabtagene autoleucel for relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b-2, open-label study. Lancet Haematol. 2022;9(12):e897-e905.	Publication reporting CARTITUDE-1 health-related quality of life (HRQOL) secondary outcomes evaluated using patient-reported outcomes (EORTC QLQ-C30, EORTC QLQ MY20, EQ-5D-5L). Follow-up to publications included in first cilta-cel submission, data with median follow-up 16·9 months.	https://www.sciencedirect.com/science/article/pii/S2352302622002848	December 2022
	CARTITUDE-1 **Janssen: Close-out analysis Clinical Study Report (CSR**) A Phase 1b-2, Open-Label Study of JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA in Subjects with Relapsed or Refractory Multiple Myeloma	This CSR provides findings at the time of study closeout for subjects treated with cilta-cel using a data release date of 14 October 2022. Follow-up to CSRs included in first cilta-cel submission, data with median follow-up 33.4 months.	N/A	Not yet published (CSR results may be published in future)