▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

CARVYKTI™

CILTACABTAGENE AUTOLEUCEL

AUSTRALIAN PRODUCT INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME

• Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving CARVYKTI. Do not administer CARVYKTI to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.

1. NAME OF THE MEDICINE

ciltacabtagene autoleucel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CARVYKTI ciltacabtagene autoleucel suspension for intravenous infusion.

A single dose of CARVYKTI is 0.5-1.0$\times 10^6$ CAR-positive viable T-cells per kg body weight up to a maximum of 1×10^8 CAR-positive viable T-cells suspended in a patient-specific infusion bag (see **section 4.2** Dosage and Method of Administration).

For a full list of excipients, see **section 6.1** List of excipients.

3. PHARMACEUTICAL FORM

Suspension for intravenous infusion

CARVYKTI (ciltacabtagene autoleucel) is a B cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy. CARVYKTI is prepared from the patient's peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure. 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, which consists of two single domain antibodies linked to 4-1BB costimulatory domain and CD3-zeta signalling domains.

The transduced anti-BCMA CAR T-cells are expanded in cell culture, washed, formulated into a suspension and cryopreserved. The product must pass a sterility test before release for shipping as a frozen suspension in a patient-specific infusion bag. The product is thawed and then infused

back into the patient, where the anti-BCMA CAR T-cells can recognize and eliminate BCMA expressing target cells.

In addition to T-cells, CARVYKTI may contain NK cells. The formulation contains 5% dimethyl sulfoxide (DMSO).

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

CARVYKTI is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody.

4.2 DOSE AND METHOD OF ADMINISTRATION

For autologous use only. For intravenous use only.

Therapy should be initiated under the direction and supervision of a healthcare professional experienced in the treatment of haematological malignancies and trained for administration and management of patients treated with ciltacabtagene autoleucel.

CARVYKTI should be administered at a certified healthcare facility. Prior to infusion ensure at least two doses of tocilizumab are available on site and emergency equipment are available for use. Ensure timely access to additional doses of tocilizumab within 8 hours of each previous dose during the recovery period.

Dose - Adults (≥18 years)

CARVYKTI is provided as a single-dose for infusion 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.

Special populations

Paediatrics (17 years of age and younger)

The safety and efficacy of CARVYKTI in children aged below 18 years of age have not been established.

No data are available.

Elderly (65 years of age and older)

No dose adjustment is required in patients ≥65 years of age.

Method of administration

Preparing Patient for CARVYKTI Infusion

Confirm availability of CARVYKTI prior to starting the lymphodepleting regimen.

Lymphodepleting regimen

Administer a lymphodepleting regimen of cyclophosphamide 300 mg/m^2 intravenously daily and fludarabine 30 mg/m^2 intravenously daily for 3 days. Administer CARVYKTI infusion 5 to 7 days after the start of the lymphodepleting regimen. If resolution of toxicities due to the lymphodepleting regimen to Grade 1 or lower takes more than 14 days, resulting in delays to CARVYKTI dosing, the lymphodepleting regimen should be re-administered after a minimum of 21 days following the first dose of the first lymphodepleting regimen. For dose modifications, see corresponding manufacturers prescribing information.

Lymphodepleting regimen must be delayed if a patient has serious adverse reactions from preceding bridging therapies (including clinically significant active infection, cardiac toxicity, and pulmonary toxicity).

Clinical assessment prior to CARVYKTI infusion

CARVYKTI infusion should be delayed if a patient has any of the following conditions:

- clinically significant active infection or inflammatory disorders.
- Grade ≥3 non-haematologic toxicities of cyclophosphamide and fludarabine conditioning except for Grade 3 nausea, vomiting, diarrhoea, or constipation. CARVYKTI infusion should be delayed until resolution of these events to Grade ≤1
- active graft versus host disease

Premedication

Administer the following pre-infusion medications to all patients (30 to 60 minutes) prior to CARVYKTI infusion:

- Antipyretics (oral or intravenous paracetamol/acetaminophen 650 to 1000 mg).
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).

Avoid use of prophylactic systemic corticosteroids as it may interfere with the activity of CARVYKTI.

Precautions to be taken before handling or administering CARVYKTI

CARVYKTI contains genetically modified human blood cells. Local biosafety guidelines applicable for handling and disposal of such products should be followed (see Special Precautions for Disposal).

CARVYKTI is prepared from autologous blood of the patient collected by leukapheresis. Patient leukapheresis material and CARVYKTI may carry a risk of transmitting infectious viruses to healthcare professionals handling the product. Accordingly, healthcare professionals should employ appropriate precautions (wearing gloves and glasses) when handling leukapheresis material or CARVYKTI to avoid potential transmission of infectious diseases as for any human derived materials.

Preparation of CARVYKTI for infusion

Do not thaw the product until it is ready to be used. Coordinate the timing of CARVYKTI thaw and infusion. Confirm the infusion time in advance and adjust the start time for thaw so that CARVYKTI is available for infusion when the patient is ready.

- Confirm patient identity: Prior to CARVYKTI preparation, match the patient's identity with the patient identifiers on the CARVYKTI cassette. Do not remove the CARVYKTI product bag from the cassette if the information on the patient-specific label does not match the intended patient.
- Once patient identification is confirmed, remove the CARVYKTI product bag from the cassette.
- Inspect the product bag for any breaches of container integrity such as breaks or cracks before thawing. Do not administer if the bag is compromised and follow the local guidelines (or contact the company).
- Place the infusion bag inside a sealable plastic bag (preferably sterile) prior to thawing.
- Thaw CARVYKTI at 37°C±2°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Total time from start of thaw until completion of thawing should be no more than 15 minutes.
- Remove the infusion bag from the sealable plastic bag and wipe dry. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain,

continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Do not pre-filter into a different container, wash, spin down, and/or resuspend CARVYKTI in new media prior to infusion.

- Once thawed, the CARVYKTI infusion must be administered and completed within 2.5 hours at room/ambient temperature (20°C to 25°C).
- Do not re-freeze or refrigerate thawed product.

Administration

- Confirm the patient's identity with the patient identifiers on the infusion bag. Do not infuse CARVYKTI if the information on the patient-specific label does not match the intended patient.
- Once thawed, administer the entire contents of the CARVYKTI bag by intravenous infusion within 2.5 hours using infusion sets fitted with an in-line filter.
- Do NOT use a leukodepleting filter.
- Gently mix the contents of the bag during CARVYKTI infusion to disperse cell clumps.
- After the entire content of the product bag is infused, flush the administration line inclusive of the in-line filter, with sodium chloride 9 mg/mL (0.9%) solution (normal saline) to ensure all product is delivered.

For special precautions for disposal, see **section 6.6** Instructions for Use and Handling and Disposal.

Monitoring after infusion

Monitor patients daily for 14 days after the CARVYKTI infusion at a certified healthcare facility and then periodically for an additional two weeks after CARVYKTI infusion for signs and symptoms of cytokine release syndrome (CRS), neurologic events and other toxicities (see **section 4.4** Special Warnings and Precautions for Use).

Instruct patients to remain within proximity of a certified healthcare facility for at least 4 weeks following infusion.

Management of Severe Adverse Reactions

Cytokine Release Syndrome

Identify CRS based on clinical presentation (see **section 4.4** Special Warnings and Precautions for Use).

If CRS is suspected, manage according to the recommendations in Table 1 Administer supportive care for CRS (including but not limited to anti-pyretic agents, IV fluid support, vasopressors, supplemental oxygen, etc.) as appropriate. Consider laboratory testing to monitor for disseminated intravascular coagulation, hematology parameters, as well as pulmonary, cardiac, renal, and hepatic function. Other monoclonal antibodies-targeting cytokines (for example, anti-IL1 and/or anti-TNFα) or therapy directed at reduction and elimination of CAR-T-cells may be considered for patients who develop high grade CRS and hemophagocytic lymphohistiocytosis (HLH), that remains severe or life-threatening following prior administration of tocilizumab and corticosteroids.

If concurrent neurologic toxicity is suspected during CRS, administer:

- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Tables 1 and 2,
- Tocilizumab according to the CRS grade in Table 1,
- Anti-seizure medication according to the neurologic toxicity in Table 2.

<table>
<tr><th colspan="3">Table 1:CRS Grading and Management Guidance</th></tr>
<tr><td>CRS Gradea</td><td>Tocilizumabb</td><td>Corticosteroidsf</td></tr>
<tr><td>Grade 1
Temperature ≥38°Cc</td><td>Tocilizumab 8 mg/kg intravenously (IV) over 1 hour (not to exceed 800 mg) may be considered</td><td>N/A</td></tr>
<tr><td rowspan="2">Grade 2
Symptoms require and respond to moderate intervention.

Temperature ≥38°Cc with:

Hypotension not requiring vasopressors,
and/or,

Hypoxia requiring oxygen via canulae or blow-by,

or,

Grade 2 organ toxicity.</td><td>Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).

Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids up to 1 litre or increasing supplemental oxygen.</td><td>Consider methylprednisolone 1 mg/kg intravenously (IV) twice daily or dexamethasone (e.g., 10 mg IV every 6 hours).</td></tr>
<tr><td colspan="2">If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose of dexamethasone (20 mg IV every 6 to 12 hours).

After 2 doses of tocilizumab, consider alternative anti-cytokine agents.d

Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.</td></tr>
<tr><td rowspan="2">Grade 3
Symptoms require and respond to aggressive intervention.

Temperature ≥38°Cc with:

Hypotension requiring one vasopressor with or without vasopressin,
and/or,

Hypoxia requiring oxygen via high-flow nasal cannulae, facemask, non-rebreather mask, or Venturi mask,

or,

Grade 3 organ toxicity or Grade 4 transaminitis.</td><td>Per Grade 2</td><td>Administer methylprednisolone 1 mg/kg IV twice daily or dexamethasone (e.g., 10 mg IV every 6 hours).</td></tr>
<tr><td colspan="2">If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose of dexamethasone (20 mg IV every 6 to 12 hours).

If no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg IV every 12 hours.

After 2 doses of tocilizumab, consider alternative anti-cytokine agents.d

Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.</td></tr>
<tr><td rowspan="2">Grade 4
Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD).

Temperature ≥38°Cc with:

Hypotension requiring multiple vasopressors (excluding vasopressin),
and/or,

Hypoxia requiring positive pressure (e.g., CPAP, BiPAP,</td><td>Per Grade 2</td><td>Administer dexamethasone 20 mg IV every 6 hours.</td></tr>
<tr><td colspan="2">After 2 doses of tocilizumab, consider alternative anti-cytokine agentsd.
Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.

If no improvement within 24 hours, consider methylprednisolone (1-2 g IV, repeat every 24 hours if needed; taper as clinically indicated) or other immunosuppressants (e.g. other anti-T cell therapies).</td></tr>
</table>

intubation, and mechanical ventilation), or, Grade 4 organ toxicity (excluding transaminitis).	

[a] Based on ASTCT 2019 grading system (Lee et.al, 2019), modified to include organ toxicity.
[b] Refer to tocilizumab prescribing information for details.
[c] Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia, as it may be masked by interventions such as antipyretics or anti-cytokine therapy (e.g., tocilizumab or steroids). Absence of fever does not impact CRS management decision. In this case, CRS management is driven by hypotension and/or hypoxia and by the more severe symptom not attributable to any other cause
[d] Monoclonal antibodies targeting cytokines may be considered based on institutional practice for unresponsive CRS.
[e] Low-flow nasal cannula is ≤6 L/min; high-flow nasal cannula is >6 L/min.
f Continue corticosteroids use until the event is Grade 1 or less; taper steroids if total corticosteroid exposure is greater than 3 days

Neurologic Toxicities

General management for neurologic toxicity e.g., Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS) is summarized in Table 2.

At the first sign of neurologic toxicity including ICANS, consider neurology evaluation. Rule out other causes of neurologic symptoms. Provide intensive care and supportive therapy for severe or life-threatening neurologic toxicities (see **section 4.4** Special Warnings and Precautions for Use).

If concurrent CRS is suspected during the neurologic toxicity event, administer:

- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Tables 1 and 2,
- Tocilizumab according to CRS grade in Table 1,
- Anti-seizure medication according to neurologic toxicity in Table 2.

Table 2:Guideline for management of ICANS	
ICANS Gradea	Corticosteroids
Grade 1 ICE score 7-9b or depressed level of consciousness: awakens spontaneously.	Consider dexamethasonec 10 mg intravenously every 6 to 12 hours for 2 to 3 days Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.
Grade 2 ICE score-3-6b or depressed level of consciousness: awakens to voice	Administer dexamethasonec 10 mg intravenously every 6 hours for 2-3 days, or longer for persistent symptoms. Consider steroid taper if total corticosteroid exposure is greater than 3 days. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.
Grade 3 ICE score-0-2b (If ICE score is 0, but the patient is arousable (e.g. awake with global aphasia) and able to perform assessment) or depressed level of consciousness: awakens only to tactile stimulus, or seizures, either:	Administer dexamethasonec10 mg-20 mg intravenously every 6 hours. If no improvement after 48 hours or worsening of neurologic toxicity, escalate dexamethasonec dose to at least 20 mg intravenously every 6 hours; taper within 7 days, OR escalate to high-dose methylprednisolone (1 g/day, repeat every 24 hours if needed; taper as clinically indicated). Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.

• any clinical seizure, focal or generalized, that resolves rapidly, or • non-convulsive seizures on EEG that resolve with intervention, or raised intracranial pressure (ICP): focal/local edema on neuroimagingd.	
Grade 4 ICE score-0b (Patient is unarousable and unable to perform ICE assessment) or depressed level of consciousness either: • patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, or seizures, either: • life-threatening prolonged seizure (>5 min), or • repetitive clinical or electrical seizures without return to baseline in between, or motor findingse: • deep focal motor weakness such as hemiparesis or paraparesis, or raised ICP / cerebral edema, with signs/symptoms such as: • diffuse cerebral edema on neuroimaging, or • decerebrate or decorticate posturing, or • cranial nerve VI palsy, or • papilledema, or • Cushing's triad	Administer dexamethasonec 10 mg-20 mg intravenously every 6 hours. If no improvement after 24 hours or worsening of neurologic toxicity, escalate to high-dose methylprednisolone (1-2 g/day, repeated every 24 hours if needed; taper as clinically indicated). Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. If raised ICP/cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g/day, repeat every 24 hours if needed; taper as clinically indicated), and consider neurology and/or neurosurgery consultation

Note: ICANS grade and management is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema), not attributable to any other cause.

[a] ASTCT 2019 criteria for grading Neurologic Toxicity (Lee et.al, 2019),

[b] If patient is arousable and able to perform Immune Effector Cell-associated Encephalopathy (ICE) Assessment, assess: Orientation (oriented to year, month, city, hospital = 4 points); Naming (name 3 objects, e.g., point to clock, pen, button = 3 points); Following Commands (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue" = 1 point); Writing (ability to write a standard sentence = 1 point); and Attention (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points.

[c] All references to dexamethasone administration are dexamethasone or equivalent

[d] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

[e] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in **Section 6.1**.

Contraindications of the lymphodepleting chemotherapy and supportive therapy should be considered

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Patients with active or prior history of significant central nervous system (CNS) disease, or inadequate renal, hepatic, pulmonary, or cardiac function are likely to be more vulnerable to the consequences of the adverse reactions described below and require special attention.

Cytokine Release Syndrome

Cytokine release syndrome, including fatal or life-threatening reactions, can occur after CARVYKTI infusion.

Nearly all patients experienced CRS after CARVYKTI infusion with majority of these being Grade 1 or Grade 2. (see **section 4.8** Adverse effects (undesirable effects)). The median time from CARVYKTI infusion (Day 1) to onset of CRS was 7 days (range of 1 to 12 days). Approximately 90% of patients experienced onset of CRS after Day 3 of receiving the CARVYKTI infusion.

In almost all cases, duration of CRS ranged from 1 to 14 days (median duration 4 days), with 88% of patients having a CRS duration of ≤ 7 days.

Clinical signs and symptoms of CRS may include but are not limited to fever (with or without rigors), chills, hypotension, hypoxia and elevated liver enzymes. Potentially life-threatening complications of CRS may include cardiac dysfunction, neurologic toxicity, and HLH. Patients who develop HLH may have an increased risk of severe bleeding. Patients should be closely monitored for signs or symptoms of these events, including fever. Risk factors for severe CRS include high pre-infusion tumour burden, active infection and early onset of fever or persistent fever after 24 hours of symptomatic treatment.

Delay the infusion of CARVYKTI if the patient has unresolved serious adverse reactions from preceding lymphodepleting or bridging therapies (including cardiac toxicity and pulmonary toxicity), rapid disease progression and clinically significant active infection (see **section 4.2** Dosing and Method of Administration). Appropriate prophylactic and therapeutic treatment for infections should be provided, and complete resolution of any active infections should be ensured prior to CARVYKTI infusion. Infections may also occur concurrently with CRS and may increase the risk of a fatal event.

Ensure that at least two doses of tocilizumab are available on site prior to infusion of CARVYKTI. Also have timely access to additional doses of tocilizumab. Monitor patients for signs and symptoms of CRS daily for 14 days after the CARVYKTI infusion at a certified healthcare facility and then periodically for an additional two weeks after CARVYKTI infusion.

Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time. At the first sign of CRS, immediately evaluate patient for hospitalisation and institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids, as indicated in Table 1 (see **section 4.2** Dosing and Method of Administration).

Evaluation for HLH should be considered in patients with severe or unresponsive CRS. For patients with high pre-infusion tumour burden, early onset of fever, or persistent fever after 24 hours, early tocilizumab should be considered. The use of myeloid growth factors, particularly granulocyte macrophage-colony stimulating factor (GM-CSF), should be avoided during CRS. Consider reducing baseline burden of disease with bridging therapy prior to infusion with CARVYKTI in patients with high tumour burden.

Neurologic toxicities

Neurologic toxicities occur frequently following treatment with CARVYKTI and can be fatal or life-threatening (see **section 4.8** Adverse effects (undesirable effects)). Neurologic toxicities included ICANS, movement and neurocognitive toxicity with signs and symptoms of parkinsonism, Guillain-Barré Syndrome, peripheral neuropathies and cranial nerve palsies. Counsel patients on the signs and symptoms of these neurologic toxicities, and on the delayed nature of onset of some of these toxicities. Instruct patients to seek immediate medical attention for further assessment and management if signs or symptoms of any of these neurologic toxicities occur at any time.

<u>Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)</u>

Patients receiving CARVYKTI may experience fatal or life-threatening ICANS following treatment with CARVYKTI, including before CRS onset, concurrently with CRS, after CRS resolution, or in

the absence of CRS. Symptoms included aphasia, slow speech, dysgraphia, encephalopathy, depressed level of consciousness and confusional state.

Consider reducing baseline burden of disease with bridging therapy prior to infusion with CARVYKTI in patients with high tumour burden, which may mitigate the risk of developing neurologic toxicity (see **section 4.8** Adverse effects (undesirable effects)). Monitor patients for signs or symptoms of ICANS for four weeks after infusion. At the first sign of ICANS, immediately evaluate patient for hospitalisation and institute treatment with supportive care as indicated in Table 2 (see **section 4.2** Dosing and Method of Administration). Early detection and aggressive treatment of CRS or ICANS may be important to prevent neurologic toxicity from occurring or worsening.

Movement and Neurocognitive Toxicity with Signs and Symptoms of Parkinsonism

Neurologic toxicity of movement and neurocognitive toxicity with signs and symptoms of parkinsonism has been reported in trials of CARVYKTI. A cluster of symptoms with variable onset spanning more than one symptom domain was observed, including movement (e.g., micrographia, tremor, bradykinesia, rigidity, stooped posture, shuffling gait), cognitive (e.g., memory loss, disturbance in attention, confusion), and personality change (e.g., reduced facial expression, flat affect, masked facies, apathy), often with subtle onset (e.g., micrographia, flat affect), that in some patients progressed to an inability to work or care for oneself. These patients all presented a combination of two or more factors such as high tumour burden (bone marrow plasma cell ≥80% or serum M-spike ≥ 5 g/dL or serum free light chain ≥ 5000 mg/L), prior Grade 2 or higher CRS, prior ICANS, and high CAR-T-cell expansion and persistence. Treatment with levodopa/carbidopa (n=2), was not effective in improving symptomatology in these patients.

Monitor patients for signs and symptoms of parkinsonism that may be delayed in onset and managed with supportive care measures.

Guillain-Barré Syndrome

Guillain-Barré Syndrome (GBS) has been reported after treatment with CARVYKTI. Symptoms reported include those consistent with Miller-Fisher variant of GBS, motor weakness, speech disturbances, and polyradiculoneuritis (see Adverse Reactions).

Monitor for GBS. Evaluate patients presenting with peripheral neuropathy for GBS. Consider treatment with intravenous immunoglobulin (IVIG) and escalate to plasmapheresis, depending on toxicity severity.

Peripheral Neuropathy

Occurrence of peripheral neuropathy, including sensory, motor, or sensorimotor, have been reported in trials of CARVYKTI.

Monitor patients for signs and symptoms of peripheral neuropathies. Consider management with short-course systemic corticosteroids, depending on the severity and progression of signs and symptoms.

Cranial Nerve Palsies

Occurrence of 7th, 3rd, 5th, and 6th cranial nerve palsy, some of which were bilateral, worsening of cranial nerve palsy after improvement, and occurrence of peripheral neuropathy in patients with cranial nerve palsy have been reported in trials of CARVYKTI.

Monitor patients for signs and symptoms of cranial nerve palsies. Consider management with short-course systemic corticosteroids, depending on the severity and progression of signs and symptoms.

Prolonged and Recurrent Cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and CARVYKTI infusion and should be managed according to local guidelines. In Study MMY2001, nearly all patients had one or more Grade 3 or 4 cytopenic adverse reactions. Most patients had a median time from infusion to first onset of Grade 3 or 4 cytopenia of less than two weeks, with

the majority of patients recovering to ≤Grade 2 by Day 30 (see **section 4.8** Adverse effects (undesirable effects)).

Monitor blood counts after CARVYKTI infusion. For thrombocytopenia, consider supportive care with transfusions. Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, particularly GM-CSF, have the potential to worsen CRS symptoms and are not recommended during the first 3 weeks after CARVYKTI or until CRS has resolved.

Serious Infections and febrile neutropenia

Serious infections, including life-threatening or fatal infections, occurred in patients after CARVYKTI infusion (see **section 4.8** Adverse effects (undesirable effects)).

Monitor patients for signs and symptoms of infection, employ surveillance testing prior to and during treatment with CARVYKTI and treat patients appropriately. Administer prophylactic antimicrobials according to local guidelines. Infections are known to complicate the course and management of concurrent CRS. Patients with clinically significant active infection should not start CARVYKTI treatment until the infection is controlled.

In the event of febrile neutropenia, infection should be evaluated and managed appropriately with broad-spectrum antibiotics, fluids and other supportive care, as medically indicated.

Patients treated with CARVYKTI may be at an increased risk of severe/fatal COVID-19 infections. Counsel patients on the importance of prevention measures.

Viral reactivation

HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients with hypogammaglobulinemia.

There is currently no experience with manufacturing CARVYKTI for patients testing positive for HIV, active HBV, or active HCV. Screening for HBV, HCV and HIV and other infectious agents must be performed in accordance with local clinical guidelines before collection of cells for manufacturing.

Hypogammaglobulinemia

Hypogammaglobulinemia may occur in patients receiving CARVYKTI.

Monitor immunoglobulin levels after treatment with CARVYKTI and administer IVIG for IgG <400 mg/dL. Manage per local clinical guidelines, including antibiotic prophylaxis or antiviral and monitoring for infection.

Live vaccines

The safety of immunisation with live viral vaccines during or following CARVYKTI treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy during CARVYKTI treatment, and until immune recovery following treatment with CARVYKTI.

Secondary Malignancies

Patients treated with CARVYKTI may develop secondary malignancies. A case of CAR positive T cell lymphoma has been reported in an ongoing study. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact the company for reporting and to obtain instructions on patient samples to collect for testing of secondary malignancy of T-cell origin. In patients with HIV infection, contact the company for the testing of all types of secondary malignancy, including those of non-T-cell origin.

Hypersensitivity

Allergic reactions may occur with infusion of CARVYKTI. Serious hypersensitivity reactions, including anaphylaxis, may be due to the dimethyl sulfoxide (DMSO), or residual kanamycin in CARVYKTI. Patients should be carefully monitored for 2 hours after infusion for signs and symptoms of severe reaction. Treat promptly and manage patients appropriately according to the severity of the hypersensitivity reaction.

Blood, organ, tissue and cell donation

Patients treated with CARVYKTI should not donate blood, organs, tissues and cells for transplantation.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed with CARVYKTI.

HIV and the lentivirus used to make CARVYKTI have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid tests (NATs) may yield false-positive results in patients who have received CARVYKTI.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on the effect of CARVYKTI on fertility. Effects of CARVYKTI on male and female fertility have not been evaluated in animal studies.

Use in pregnancy

Category C

There are no available data on the use of CARVYKTI in pregnant women. No reproductive and developmental toxicity animal studies have been conducted with CARVYKTI. It is not known whether CARVYKTI has the potential to be transferred to the foetus and cause foetal toxicity. Therefore, CARVYKTI is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women should be advised there may be risks to the foetus. Pregnancy after CARVYKTI therapy should be discussed with the treating physician.

Pregnant women who have received CARVYKTI may have hypogammaglobulinemia. Assessment of immunoglobulin levels in new-borns of mothers treated with CARVYKTI should be considered.

Pregnancy status for females of child-bearing age should be verified prior to starting treatment with CARVYKTI.

There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with CARVYKTI.

In clinical trials, female patients of childbearing potential were advised to practice a highly effective method of contraception, and male patients with partners of childbearing potential or whose partners were pregnant, were instructed to use a barrier method of contraception until one year after the patient has received CARVYKTI infusion.

See the prescribing information for lymphodepleting chemotherapy for information on the need for contraception in patients who receive the lymphodepleting chemotherapy.

Use in lactation

There is no information regarding the presence of CARVYKTI in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CARVYKTI and any potential adverse effects on the breastfed infant from CARVYKTI or from the underlying maternal condition.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Due to the potential for neurologic events, patients receiving CARVYKTI are at risk for altered or decreased consciousness or coordination in the 8 weeks following CARVYKTI infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery during this initial period, and in the event of new onset of any neurological symptoms.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety of CARVYKTI was evaluated in 187 adult patients with multiple myeloma infused with CARVYKTI in two open label clinical trials: Study MMY2001 (N=106), which included patients from the main Phase 1b/2 cohort (United States; n=97; with a median duration of follow-up of 18 months) and an additional cohort (Japan; n=9), and Study MMY2003 (n=81).

The most common CARVYKTI adverse reactions (≥20%) were neutropenia, CRS, pyrexia, anaemia, thrombocytopenia, leukopenia, lymphopenia, hypotension, transaminase elevation, musculoskeletal pain, fatigue, upper respiratory tract infection, cough, hypocalcaemia, diarrhoea, hypophosphatemia, chills, nausea, decreased appetite, tachycardia, headache, oedema, encephalopathy and hypokalaemia,

Serious adverse reactions occurred in 45% of patients; serious adverse reactions reported in ≥5% of patients were CRS (17%), sepsis (6%), ICANS (5%), encephalopathy (5%), and neutropenia (5%).

The most common (≥10%) Grade ≥ 3 non-haematological adverse reactions was transaminase elevation (16%).

The most frequent (≥25%) Grade ≥3 haematological abnormalities were neutropenia (93%), leukopenia (54%), anaemia (57%), thrombocytopenia (51%) and lymphopenia (44%).

Tabulated list of adverse reactions

Table 3 summarises the adverse reactions that occurred in patients receiving CARVYKTI.

Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000); not known (cannot be estimated from the available data).

Table 3: Adverse reactions in patients with multiple myeloma treated with CARVYKTI (N=187)

System Organ Class	Frequency	Adverse Reaction	Incidence (%)	
			All Grades	Grade ≥ 3
Infections and infestations	Very common	Upper respiratory tract infection[1]	35	3
		Bacterial infection[2#]	11	4
	Common	Sepsis[3#]	9	7
		Pneumonia[4#]	8	7
		Viral infection[5]	5	2
		Fungal infection[6]	3	1
		Cytomegalovirus infection[7]	2	2
Blood and lymphatic system disorders	Very common	Neutropenia	94	93
		Anemia	73	57
		Thrombocytopenia	74	51
		Leukopenia	55	54
		Lymphopenia	46	44
		Coagulopathy[8]	15	2
		Febrile neutropenia	13	12
		Hypofibrinogenemia[9]	12	3

Immune system disorders	Very common	Cytokine release syndrome[#]	89	4
		Hypogammaglobulinaemia[10]	11	1
	Common	Haemophagocytic lymphohistiocytosis[#]	3	2
Metabolism and nutrition disorders	Very common	Hypocalcaemia	27	5
		Hypophosphataemia	25	7
		Decreased appetite	21	2
		Hypoalbuminaemia	18	1
		Hyponatraemia	19	4
		Hypokalaemia	20	3
		Hypomagnesaemia	16	0
Psychiatric disorders	Common	Insomnia	9	0
		Delirium[11]	5	1
		Personality changes[12]	4	1
Nervous system disorders	Very common	Headache	26	0
		Encephalopathy[13]	23	5
		Motor dysfunction[14]	17	5
		Dizziness[15]	17	1
		Immune effector cell-associated neurotoxicity syndrome[#]	16	3
		Neuropathy peripheral[16]	12	3
	Common	Aphasia[17]	7	1
		Tremor[18]	6	0
		Ataxia[19]	6	1
		Cranial nerve palsies[20]	5	1
		Paresis[21]	2	1
		Neurotoxicity[#]	2	2
		Guillain-Barre syndrome	1	1
Cardiac disorders	Very common	Tachycardia[22]	22	1
	Common	Cardiac arrhythmias[23]	6	2
Vascular disorders	Very common	Hypotension[24]	42	7
		Hypertension	15	4
	Common	Haemorrhage[25]	8	2
		Thrombosis[26]	6	1
Respiratory, thoracic and mediastinal disorders	Very common	Cough[27]	26	0
		Dyspnoea[28#]	19	4
		Hypoxia[29]	13	5
Gastrointestinal disorders	Very common	Diarrhoea	30	2
		Nausea	27	1
		Constipation	18	0
		Vomiting	18	0
		Abdominal pain[30]	10	0
Hepatobiliary disorders	Common	Hyperbilirubinemia	5	2
Skin and subcutaneous tissue disorders	Common	Rash[31]	9	0
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain[32]	44	4
Renal and urinary disorders	Common	Renal failure[33]	7	4
General disorders and administration site conditions	Very common	Pyrexia	89	6
		Fatigue[34]	41	6
		Chills	22	0
		Oedema[35]	23	2
		Pain[36]	13	1

Investigations	Very common	Transaminase elevation[37]	37	16
		Gamma-glutamyltransferase increased	14	8
		Blood alkaline phosphatase increased	11	3
		Blood lactate dehydrogenase increased	11	0
		Serum ferritin increased	12	3
	Common	C-reactive protein increased	8	2

Adverse events are reported using MedDRA version 23.0

Contains fatal event/s.

1 Upper respiratory tract infection includes Bronchitis, Nasal congestion, Nasopharyngitis, Paranasal sinus discomfort, Pharyngeal inflammation, Respiratory tract congestion, Rhinitis, Rhinorrhoea, Rhinovirus infection, Sinus congestion, Sinusitis, Upper respiratory tract infection, and Viral upper respiratory tract infection.

2 Bacterial infection includes Abscess limb, Breast cellulitis, Campylobacter infection, Cellulitis, Citrobacter infection, Clostridium difficile colitis, Clostridium difficile infection, Device related infection, Ecthyma, Enterococcal infection, Folliculitis, Hordeolum, Klebsiella infection, Lung abscess, Osteomyelitis, Perirectal abscess, Skin infection, Staphylococcal infection, and Tooth infection.

3 Sepsis includes Bacteraemia, Bacterial sepsis, Enterococcal bacteremia, Pseudomonal bacteraemia, Sepsis, Septic shock, Staphylococcal bacteraemia and Streptococcal sepsis.

4 Pneumonia includes Atypical pneumonia, COVID-19 pneumonia, Pneumocystis jirovecii pneumonia, Pneumonia, and Pneumonia aspiration..

5 Viral infection includes Adenovirus test positive, COVID-19, Coronavirus infection, Influenza, and Parainfluenzae virus infection

6 Fungal infection includes Aspergillus infection, Candida infection, Cerebral aspergillosis, Oral candidiasis, Sinusitis aspergillus, and Tongue fungal infection..

7 Cytomegalovirus infection includes Cytomegalovirus syndrome, and Cytomegalovirus viraemia.

8 Coagulopathy includes Activated partial thromboplastin time prolonged, Coagulopathy, Disseminated intravascular coagulation, Fibrin D dimer increased, International normalised ratio increased, Prothrombin level increased, and Prothrombin time prolonged.

9 Hypofibrinogenemia includes Blood fibrinogen decreased, and Hypofibrinogenaemia.

10 Hypogammaglobulinemia includes Blood immunoglobulin G decreased, and Hypogammaglobulinemia

11 Delirium includes Agitation, Delirium, Euphoric mood, Hallucination, Irritability, and Restlessness.

12 Personality changes includes Apathy, Flat affect, Indifference, Personality change, and Reduced facial expression.

13 Encephalopathy includes Amnesia, Bradyphrenia, Cognitive disorder, Confusional state, Depressed level of consciousness, Disturbance in attention, Encephalopathy, Lethargy, Memory impairment, Mental impairment, Mental status changes, Psychomotor retardation, Sleep disorder, and Somnolence.

14 Motor dysfunction includes Agraphia, Bradykinesia, Cogwheel rigidity, Dysgraphia, Eyelid ptosis, Micrographia, Motor dysfunction, Muscle rigidity, Muscle spasms, Muscle tightness, Muscular weakness, Myoclonus, Parkinsonism, Posture abnormal, and Stereotypy.

15 Dizziness includes Dizziness, Dizziness exertional, Presyncope, Syncope, and Vertigo.

16 Neuropathy peripheral includes Hypoaesthesia, Neuralgia, Paraesthesia, Paraesthesia ear, Peripheral motor neuropathy, Peripheral sensorimotor neuropathy Peripheral sensory neuropathy, Polyneuropathy and Sensory loss.

17 Aphasia includes Aphasia, Dysarthria, Slow speech, and Speech disorder.

18 Tremor includes Resting tremor, and Tremor.

19 Ataxia includes Ataxia, Balance disorder, and Gait disturbance.

20 Cranial nerve palsies includes Bell's palsy, Cranial nerve paralysis, Facial nerve disorder, Facial paralysis, Facial paresis, and VIth nerve paralysis.

21 Paresis includes Hemiparesis, Paresis, and Peroneal nerve palsy

22 Tachycardia includes Sinus tachycardia, and Tachycardia.

23 Cardiac arrhythmias includes Atrial fibrillation, Atrial flutter, Supraventricular tachycardia, Ventricular extrasystoles, and Ventricular tachycardia.

24 Hypotension includes Hypotension, and Orthostatic hypotension.

25 Hemorrhage includes Conjunctival haemorrhage, Epistaxis, Haemoptysis, Post procedural haemorrhage, Pulmonary haemorrhage, Retinal haemorrhage and Subarachnoid hemorrhage.

26 Thrombosis includes Cerebrovascular accident, Deep vein thrombosis, Device related thrombosis, Embolism, Jugular vein thrombosis, and Pulmonary embolism.

27 Cough includes Cough, Productive cough, and Upper-airway cough syndrome.

28 Dyspnea includes Acute respiratory failure, Dyspnea, Dyspnea exertional, Respiratory failure, and Wheezing.

29 Hypoxia includes Hypoxia, Oxygen consumption decreased and Oxygen saturation decreased.

30 Abdominal pain includes Abdominal discomfort, Abdominal pain, Abdominal pain upper, and Dyspepsia.

31 Rash includes Dermatitis exfoliative generalized, Erythema, Rash, Rash erythematous, Rash maculo-papular, Rash pustular, and Rash vesicular

32 Musculoskeletal pain includes Arthralgia, Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal discomfort, Musculoskeletal pain, Musculoskeletal stiffness, Myalgia, Neck pain, and Pain in extremity.

33 Renal failure includes Acute kidney injury, Blood creatinine increased, and Chronic kidney disease.

34 Fatigue includes Asthenia, Exercise tolerance decreased, Fatigue, and Malaise.

35 Oedema includes Face oedema, Fluid retention, Generalised oedema, Hypervolemia Joint swelling, Localised oedema, Oedema, Oedema peripheral, Palatal oedema, Periorbital oedema, Peripheral swelling, Pulmonary congestion, Pulmonary oedema, and Scrotal oedema.

36 Pain includes Catheter site pain, Ear pain, Eye pain, Fracture pain, Non-cardiac chest pain, Odynophagia, Pain, Pain in jaw, Proctalgia, Rhinalgia, Sacral pain, Sinus pain, Testicular pain and Toothache.

37 Transaminase elevation includes Alanine aminotransferase increased, and Aspartate aminotransferase increased.

Description of selected adverse reactions

Cytokine release syndrome

In Study MMY2001 (N=97), CRS was reported in 95% of patients (n=92); 90% (n=87) CRS events were Grade 1 or Grade 2, 4% (n=4) Grade 3 or 4, and 1% (n=1) was Grade 5. Ninety-nine percent of patients (n=91) recovered from CRS.

The duration of CRS was ≤14 days for all but one patient who had a duration of CRS of 97 days, complicated by secondary HLH with a subsequent fatal outcome. The most frequent (≥10%) signs or symptoms associated with CRS included pyrexia (95%), hypotension (41%), Aspartate aminotransferase (AST) increased (21%), chills (14%), Alanine aminotransferase (ALT) increased (13%) and sinus tachycardia (10%). See **section 4.4** Special Warnings and Precautions for Use for monitoring and management guidance.

Neurologic toxicities

In Study MMY2001 (N=97), neurologic toxicity occurred in 22% (n=21) of patients with 9% (n=9) being Grade 3 or Grade 4 and 2% Grade 5 (n=2; one due to ICANS, one due to movement and neurocognitive toxicity with signs and symptoms of parkinsonism). In addition, three patients had fatal outcomes with ongoing neurologic toxicity at the time of death; two deaths were due to infection in patients with ongoing signs and symptoms of parkinsonism, as discussed below, and one death was due to respiratory failure.

Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

ICANS occurred in 18% of patients (n=17), with 2% (n=2) experiencing Grade 3 or Grade 4 ICANS and 1% (n=1) Grade 5 ICANS. . The median time from CARVYKTI infusion to first onset of ICANS was 8.0 days (range: 3 to 12 days, except for 1 patient with onset at 26 days) and the median duration was 4 days (range: 1 to 12 days, except for 1 patient who had a subsequent fatal outcome at 40 days).

Movement and Neurocognitive Toxicity with Signs and Symptoms of Parkinsonism

Of the 21 patients in Study MMY2001 experiencing any neurotoxicity, five male patients had neurologic toxicity with several signs and symptoms of parkinsonism, distinct from ICANS. The maximum toxicity grades of parkinsonism were: Grade 2 (n=1) and Grade 3 (n=4). The median onset of parkinsonism was 27 days (range: 14 to 108 days) from infusion of CARVYKTI. One patient (Grade 3) died of neurologic toxicity with ongoing parkinsonism 247 days after administration of CARVYKTI, and two patients (Grade 2 and Grade 3) with ongoing parkinsonism died of infectious causes 162 and 119 days after administration of CARVYKTI. In the remaining 2 patients (Grade 3), symptoms of parkinsonism were ongoing up to 530 days after administration of CARVYKTI. All 5 patients had a history of prior CRS (n=4 Grade 2; n=1 Grade 3), while 4 of 5 patients had prior ICANS (n=4 Grade 1).

In another study (Study MMY2003), one male patient experienced neurotoxicity with signs and symptoms of parkinsonism after treatment with CARVYKTI. This patient had experienced Grade 4 CRS after CARVYKTI infusion.

Guillain-Barré Syndrome

In another study (Study MMY2003), one patient was reported to have GBS after treatment with CARVYKTI. Although GBS symptoms improved after receiving treatment with steroids and IVIG, the patient died 139 days after administration of CARVYKTI due to encephalopathy post gastroenteritis with ongoing GBS symptoms.

Peripheral Neuropathy

In Study MMY2001, six patients developed peripheral neuropathy, presenting as sensory, motor, or sensorimotor neuropathies. Median time of onset of symptoms was 62 days (range: 4 to 136 days), median duration of peripheral neuropathies was 256 days (range: 2 to 465 days) including those with ongoing neuropathy. Of these 6 patients, 2 experienced Grade 3 peripheral neuropathy (1 of which resolved with no treatment reported, and the other improved after treatment with

dexamethasone); of the remaining 4 with ≤ Grade 2 peripheral neuropathy, peripheral neuropathy resolved with no treatment reported in 2 patients, and was ongoing in the other 2 patients.

Cranial Nerve Palsies

In Study MMY2001, three patients experienced cranial nerve palsies. Median time to onset was 26 days (range: 21 to 101 days) following infusion of CARVYKTI, and median time to resolution was 70 days (range: 1 to 79 days) following onset of symptoms.

Prolonged and recurrent cytopenias

In Study MMY2001 (N=97), Grade 3 or higher cytopenias at Day 1 after dosing, not resolved to Grade 2 or lower by Day 30 following CARVYKTI infusion, included thrombocytopenia (41%), neutropenia (30%), and lymphopenia (12%). After Day 60 following CARVYKTI, 31%, 12%, and 6% of patients had an occurrence of Grade 3 or higher lymphopenia, neutropenia and thrombocytopenia respectively, after initial recovery of their Grade 3 or Grade 4 cytopenia.

Table 4 lists the incidences of Grade 3 or Grade 4 cytopenias occurring after dosing not resolved to Grade 2 or lower by Day 30 and Day 60 respectively.

Table4: Incidences of Prolonged and Recurrent Cytopenias Following Treatment with CARVYKTI in Study MMY2001 (N=97)

	Grade 3/4 (%) After Day 1 Dosing	Initial Grade 3/4 (%) Not Recovered[a] to ≤Grade 2 by Day 30	Initial Grade 3/4 (%) Not Recovered[a] to ≤Grade 2 by Day 60	Occurrence of Grade 3/4 (%) > Day 60 (after Initial Recovery[a] of Grade 3/4)
Thrombocytopenia	60 (62%)	40 (41%)	25 (26%)	6 (6%)
Neutropenia	95 (98%)	29 (30%)	10 (10%)	12 (12%)
Lymphopenia	96 (99%)	12 (12%)	8 (8%)	30 (31%)

[a] The laboratory result with the worst toxicity grade will be used for a calendar day. Recovery definition: must have 2 consecutive Grade ≤2 results on different days if recovery period ≤10 days.
Notes: Lab results assessed after Day 1 until Day 100 are included in the analysis.
Thrombocytopenia: Grade 3/4 – Platelets count <50000 cells/µL.
Neutropenia: Grade 3/4 - Neutrophil count <1000 cells/µL.
Lymphopenia: Grade 3/4 - Lymphocytes count $<0.5 \times 10^9$ cells/L.
Percentages are based on the number of treated subjects

Serious infections

Infections occurred in 56 patients (58%) in Study MMY2001 (N=97); 19 (20%) experienced Grade 3 or Grade 4 infections, and fatal infections occurred in 3 patients (3%); lung abscess, sepsis, and septic shock. The most frequently reported (≥5%) Grade 3 or higher infections were pneumonia and sepsis. Febrile neutropenia was observed in 10% of patients with 4% experiencing serious febrile neutropenia. See **section 4.4** Special Warnings and Precautions for Use for monitoring and management guidance.

Hypogammaglobulinemia

In Study MMY2001 (N=97) hypogammaglobulinemia was reported in 12% of patients with 2% of patients experiencing Grade 3 or Grade 4 hypogammaglobulinemia laboratory IgG levels fell below 500 mg/dL after infusion in 92% (89/97) of patients treated with CARVYKTI. Hypogammaglobulinemia either as an adverse reaction or a laboratory IgG level below 500 mg/dL, after CARVYKTI infusion occurred in 94% (91/97) of patients. Thirty-eight percent of patients received IVIG post CARVYKTI for either an adverse reaction or prophylaxis. See **section 4.4** Special Warnings and Precautions for Use for monitoring and management guidance.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Treatment

There are no data regarding the signs or sequelae of overdose with CARVYKTI. For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

CARVYKTI is a BCMA-directed, genetically modified autologous T cell immunotherapy, which involves reprogramming a patient's own T-cells with a transgene encoding a chimeric antigen receptor (CAR) that identifies and eliminates cells that express BCMA. BCMA is primarily expressed on the surface of malignant multiple myeloma B-lineage cells, as well as late-stage B cells and plasma cells. The CARVYKTI CAR protein features two BCMA-targeting single domain antibodies designed to confer high avidity against human BCMA, a 4-1BB co-stimulatory domain and a CD3-zeta (CD3ζ) signalling cytoplasmic domain. Upon binding to BCMA expressing cells, the CAR promotes T-cell, activation, expansion and elimination of target cells.

In vitro co-culture experiments demonstrated that ciltacabtagene autoleucel-mediated cytotoxicity and cytokine release (interferon-gamma, [IFN-γ], tumour necrosis factor alpha [TNF-α], interleukin [IL]-2) were BCMA-dependent.

Pharmacodynamic effects

After a single infusion of CARVYKTI, expansion of CAR positive T-cells coincided with decreases of serum soluble BCMA, serum M-protein, and/or free light chains. Across all patients, levels of IL-6, IL-10, IFN-γ and lL-2 receptor alpha increased post-infusion and peaked at Days 7-14. The serum levels of all cytokines generally returned to baseline levels within 2-3 months post-infusion.

Immunogenicity

The immunogenicity of CARVYKTI has been evaluated using a validated assay for the detection of binding antibodies against CARVYKTI pre-dose and at multiple timepoints post-infusion. In Study MMY2001, 19 of 97 patients (19.6%) were positive for anti-CAR antibodies.

There was no clear evidence to suggest that the observed anti-CAR antibodies impact CARVYKTI kinetics of initial expansion and persistence, efficacy or safety.

Clinical trials

MMY2001 was an open label trial evaluating CARVYKTI for the treatment of patients with relapsed or refractory multiple myeloma, who previously received a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and who had disease progression on or after the last regimen.

In total, 113 patients underwent leukapheresis; CARVYKTI was manufactured for all patients. The median time from the day after receipt of leukapheresis material at manufacturing facility to release of product for infusion was 29 days (range: 23 to 64 days) and the median time from initial leukapheresis to CARVYKTI infusion was 47 days (range: 41 days to 167 days).

Following leukapheresis and prior to administration of CARVYKTI, 73 of the 97 patients (75%) received bridging therapy. The most commonly used agents as bridging therapies (≥20% of patients) included dexamethasone: 62 patients (64%), bortezomib: 26 patients (27%), cyclophosphamide: 22 patients (23%), and pomalidomide: 21 patients (22%).

CARVYKTI was administered as a single IV infusion 5 to 7 days after the start of a lymphodepleting chemotherapy (cyclophosphamide 300 mg/m2 intravenously daily and fludarabine 30 mg/m^2 intravenously daily for 3 days). Ninety-seven patients received CARVYKTI at a median dose of 0.71×10^6 CAR-positive viable T-cells/kg (range: 0.51 to 0.95×10^6 cells/kg). All patients were hospitalized for CARVYKTI infusion and for a minimum of 10 days afterward. Sixteen patients were not treated with CARVYKTI (n=12 after leukapheresis and n=4 after lymphodepleting therapy), due to either withdrawal by patient (n=5), progressive disease (n=2) or death (n=9).

Of the 97 patients treated, 59% were male, 71% were Caucasian and 18% were African-American. The median patient age was 61 years (range: 43 to 78 years). Patients had received a median of 6 (range: 3 to 18) prior lines of therapy and 90% of patients had received prior autologous stem cell transplantation (ASCT). Ninety-nine percent of patients were refractory to their last line of prior therapy and 88% were refractory to a proteasome inhibitor (PI), immunomodulatory agent, and anti-CD38 antibody.

Patients with known active, or prior history of significant central nervous system (CNS) disease, including CNS multiple myeloma, allogenic stem cell transplant within 6 months before apheresis or ongoing treatment with immunosuppressants, creatinine clearance < 40mL/min, absolute lymphocyte concentration < 300/µL, hepatic transaminases > 3 times the upper limit of normal, cardiac ejection fraction < 45%, or with active serious infection were excluded from the trial.

Efficacy results were based on overall response rate as determined by the Independent Review Committee assessment using IMWG criteria (see Table 5).

Table 5:Efficacy results for Study MMY2001	
	All Treated (N=97)
Overall Response Rate (sCR[a] + VGPR + PR) n (%) 95% CI (%)	95 (97.9) (92.7, 99.7)
Stringent complete response (sCR[a]) n (%)	78 (80.4)
Very good partial response (VGPR) n (%)	14 (14.4)
Partial response (PR) n (%)	3 (3.1)
Duration of Response (DOR)	
Number of responders DOR (Months)[:] Median (95% CI)	95 21.8 (21.8, NE)
Number of responders with sCR[a] DOR if best response is sCR[a] (Months):Median (95% CI)	78 NE (21.8, NE)
Number of responders with VGPR or better DOR if best response is VGPR or better (Months): Median (95% CI)	92 21.8 (21.8, NE)
Time to Response (months)	
Number of responders Median Range	95 0.95 (0.9; 10.7)
Time to sCR[a] (months)	
Number of responders with sCR[a] Median Range	78 2.63 (0.9; 15.2)

Notes: Based on a median duration of follow up of 18 months

[a] All complete responses were stringent CRs

Table 6:Summary of MRD negativity rate

	All Treated (N=97)
MRD negativity rate n (%) 95% CI (%)	56 (57.7) (47.3, 67.7)
MRD negative patients with sCRn (%)[a] 95% CI (%)	42 (43.3) (33.3. 53.7)
	Evaluable patients (N=61)
MRD negativity rate n (%)	56 (91.8)
95% CI (%)	(81.9, 97.3)

MRD= Minimal Residual Disease

Notes:Based on a median duration of follow up of 18 months

[a] Only MRD assessments (10^{-5} testing threshold) within 3 months of achieving CR/sCR until death / progression / subsequent therapy (exclusive) are considered. All complete responses were stringent CRs

With a median duration of follow up of 18 months, median Progression Free Survival (PFS) was 22.8 months (95% CI: 22.8, not estimable). The 12-month PFS rate (95% CI) was 76.3% (66.5%, 83.6%).

For patients who achieved sCR (all complete responses were stringent CRs), median PFS was not reached (95% CI: 22.8%, not estimable) with an estimated 12-month PFS rate of 88.5% (95% CI: 79.0%, 93.8%).

Median overall survival (OS) was not reached (95% CI: 23.59%, not estimable). The OS rate at 12 months was 87.6% (95% CI: 79.2%, 92.8%).

Health-related quality of life (HRQoL) was evaluated by the EORTC QLQ-C30 and completed at baseline (n=63) and during the post-infusion phase. The adjusted mean (95% CI) change from baseline in the EORTC QLQ-C30 Pain subscale was -1.9 (-8.5, -4.6) at Day 7, -9.9 (-16.5, -3.3) at Day 28, -6.3 (-12.9, -0.4) on Day 56, -9.4 (-16.3, -2.5) at Day 78, and -10.5 (-17.3, -3.8) on Day 100, indicating overall reduction in pain following CARVYKTI infusion. Clinically, meaningful improvements at Day 100 were seen in 72.2% of patients for the pain subscale, 53.8% for the

fatigue subscale, 57.7% for the physical functioning subscale, and 53.7% for the global health status subscale.

MAMMOTH analysis

A retrospective, patient-level, pooled analysis of outcomes of patients with multiple myeloma refractory to CD38 monoclonal antibodies was conducted to provide context for interpreting the efficacy results reported in Study MMY2001.

From the MAMMOTH dataset, the analysis identified a patient population (N=122). corresponding to the Study MMY2001 all-treated population.

For the patients from the MAMMOTH dataset, Day 1 of the study was 47 days after the start of standard of care conventional therapy.

For the patients from the MAMMOTH dataset, the overall response rate (ORR) was 38%, 12-month PFS rate (95% CI) was 7% (1%,13%), and 12-month OS rate (95% CI) was 40% (30%, 50%).

The MAMMOTH retrospective outcomes analysis indicated that patients receiving CARVYKTI (Study MMY2001) had better outcomes than patients receiving other available treatments assessed in the MAMMOTH study, as measured by ORR, PFS and OS.

5.2 PHARMACOKINETIC PROPERTIES

CARVYKTI pharmacokinetics (PK) was assessed in 97 patients with multiple myeloma receiving a single CARVYKTI infusion at the median dose of 0.71×10^6 CAR positive viable T-cells/kg (range: 0.51×10^6 to 0.95×10^6 cells/kg).

Following a single infusion, CARVYKTI exhibited an initial expansion phase followed by a rapid decline and then a slower decline. However, high interindividual variability was observed.

Table 7: Pharmacokinetic Parameters of CARVYKTI in patients with multiple myeloma

Parameter	Summary Statistics	N=97
C_{max} (copies/µg genomic DNA)	Mean (SD), n	48692 (27174), 97
t_{max} (day)	Median (range), n	12.71 (8.73 – 329.77), 97
$AUC_{0\text{-}28d}$ (copies*day/µg genomic DNA)	Mean (SD), n	504496 (385380), 97
$AUC_{0\text{-}last}$ (copies*day/µg genomic DNA)	Mean (SD), n	109803 (1387010), 97
$AUC_{0\text{-}6m}$ (copies*day/µg genomic DNA)	Mean (SD), n	1033373 (135539), 96
$t_{1/2}$ (day)	Mean (SD), n	23.5 (24.2), 42
t_{last} (day)	Median (range), n	125.90 (20.04 – 702.12), 97

After the cell expansion, the persistence phase of the CARVYKTI levels was observed for all patients. At the time of analysis (n=65), the median time for CAR transgene levels in peripheral blood to return to the pre-dose baseline level was approximately 100 days (range: 28 to 365 days) post-infusion.

Detectable CARVYKTI exposures in bone marrow indicate a distribution of CARVYKTI from systemic circulation to bone marrow. Similar to blood transgene levels, bone marrow transgene levels declined over time and exhibited high interindividual variability.

Some patients required tocilizumab, corticosteroids and anakinra for management of CRS. CARVYKTI continues to expand and persist following tocilizumab administration. Patients treated with tocilizumab (n=68) had 81% and 72% higher CARVYKTI C_{max} and $AUC_{0\text{-}28d}$, respectively, as compared to patients (n=29) who did not receive tocilizumab. Patients who received corticosteroids (n=28) had 75% and 112% higher C_{max} and $AUC_{0\text{-}28d}$, respectively, compared with patients who did not receive corticosteroids (n=69). In addition, patients who received anakinra (n=20) had 41% and 72% higher C_{max} and $AUC_{0\text{-}28d}$, respectively, compared with patients who did not receive anakinra (n=77).

Special populations

The pharmacokinetics of CARVYKTI (C_{max} and $AUC_{0\text{-}28d}$) were not impacted by age (range: 43 to 78 years), including patients <65 years of age [n=62; 63.9%], 65-75 years (n=27; 27.8%) and >75 years of age (n=8; 8.2%).

Similarly, the pharmacokinetics of CARVYKTI (C_{max} and $AUC_{0\text{-}28d}$) were not impacted by gender, body weight, and race.

Renal impairment

Renal impairment studies of CARVYKTI were not conducted. CARVYKTI C_{max} and $AUC_{0\text{-}28d}$ were similar in patients with mild renal dysfunction (60 mL/min ≤ creatinine clearance [CRCL] < 90 mL/min), and in patients with normal renal function (CRCL ≥ 90 mL/min).

Hepatic impairment

Hepatic impairment studies of CARVYKTI were not conducted. CARVYKTI C_{max} and $AUC_{0\text{-}28d}$ were similar in patients with mild hepatic dysfunction [(total bilirubin ≤upper limit of normal (ULN) and aspartate aminotransferase >ULN) or (ULN < total bilirubin ≤ 1.5 times ULN)] and patients with normal hepatic function.

5.3 PRECLINICAL SAFETY DATA

Nonclinical safety assessment of CARVYKTI confirmed the on-target specificity of CARVYKTI to BCMA.

Genotoxicity

No genotoxicity studies have been performed.

The risk for insertional mutagenesis occurring during the manufacturing of ciltacabtagene autoleucel following transduction of autologous human T-cells with an integrating lentiviral vector (LV) was assessed by evaluating the integration pattern of the vector in pre-infusion CARVYKTI. This genomic insertional site analysis was performed on CARVYKTI products from 7 patients and 3 healthy volunteers. There was no evidence for preferential integration near genes of concern.

The potential for enhanced proliferation of CARVYKTI was assessed in an in vitro cytokine independent growth assay. Integration of LV into primary T cell genome during transduction did not lead to cytokine independent uncontrolled growth in the absence of IL-2 (the cytokine that regulates T-cell growth and promotes T-cell survival) of CARVYKTI.

Carcinogenicity

No carcinogenicity studies have been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Cryostor CS5, which contains dimethyl sulfoxide.

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

See expiry date on the outer pack.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store and transport below -120°C, e.g., in a container for cryogenic storage in the vapour phase of liquid nitrogen.

Store in the original packaging containing the cassette protecting the infusion bag.

Once thawed, the product should be administered immediately and the infusion should be completed within 2.5 hours at room/ambient temperature (20°C to 25°C). Thawed product should not be shaken, refrozen or refrigerated.

6.5 NATURE AND CONTENTS OF CONTAINER

Ethylene vinyl acetate (EVA) 30 mL or 70 mL infusion bag with sealed addition tube and two available spike ports.

Each infusion bag is individually packed in an aluminium cryo cassette.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Do not irradiate as this could lead to inactivation of the product.

CARVYKTI should be transported within the facility in closed, break-proof, leak-proof containers.

Unused CARVYKTI must be disposed of in compliance with local guidelines for the disposal of medicinal products containing genetically modified cells. All material that has been in contact with CARVYKTI (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local biosafety guidelines.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

CARVYKTI (ciltacabtagene autoleucel) is a B cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy. CARVYKTI is prepared from the patient's peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure. Consequently, a defined structure is not available for ciltacabtagene autoleucel.

CAS number

No data available.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Class 4 Biological

8. SPONSOR

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9. DATE OF FIRST APPROVAL

6 June 2023

10. DATE OF REVISION

28 February 2024

Summary table of changes

Section changed	Summary of new information
4.4	Added new text in subsection on secondary malignancies