ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

CARVYKTI $3.2 \times 10^6 – 1 \times 10^8$ cells dispersion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

CARVYKTI (ciltacabtagene autoleucel) is a genetically modified autologous cell-based product, containing T cells transduced *ex vivo* using a replication incompetent lentiviral vector encoding an anti-B cell maturation antigen (BCMA) chimeric antigen receptor (CAR), comprising two single domain antibodies linked to a 4-1BB costimulatory domain and a CD3-zeta signaling domain.

2.2 Qualitative and quantitative composition

Each patient-specific infusion bag of CARVYKTI contains ciltacabtagene autoleucel at a batch-dependent concentration of autologous T cells genetically modified to express an anti-BCMA chimeric antigen receptor (CAR-positive viable T cells) (see section 4.2). The medicinal product is packaged in one infusion bag containing a cell dispersion for infusion of 3.2×10^6 to 1×10^8 CAR-positive viable T cells suspended in a cryopreservative solution.

An infusion bag contains 30 mL or 70 mL of dispersion for infusion.

The cellular composition and the final cell number is dependent on patient body weight and varies between individual patient batches. In addition to T cells, Natural Killer (NK) cells may be present.

The quantitative information of the medicinal product including the total viable cell concentration, volume of dispersion and total number of CAR+ cells per bag and supplied dose is presented in the Lot Information Sheet included with the cryo cassette used for transport of CARVYKTI.

Excipient(s) with known effect
Each dose of CARVYKTI contains 0.05 mL of dimethyl sulfoxide (DMSO) per mL and residual kanamycin (see section 4.4).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for infusion
A colourless to white, including shades of white, yellow, and pink, dispersion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

CARVYKTI must be administered in a qualified treatment centre.
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 CARVYKTI.
Prior to infusion, the qualified treatment centre must have at least 1 dose of tocilizumab available for use in the event of cytokine release syndrome (CRS), with access to an additional dose within 8 hours of each previous dose (see section 4.4). In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, suitable alternative measures to treat CRS instead of tocilizumab must be available prior to infusion.
Emergency equipment must be available prior to infusion and during the recovery period.

Posology

CARVYKTI is intended for autologous use (see section 4.4).

Treatment consists of a single dose for infusion containing a dispersion of CAR-positive viable T cells in one infusion bag.
The target dose is 0.75 x 10^6 CAR-positive viable T cells/kg of body weight (not exceeding 1×10^8 CAR-positive viable T cells).

Patients 100 kg and below: 0.5 - 1 x 10^6 CAR-positive viable T cells/kg body weight.
Patients above 100 kg: 0.5 - 1 x 10^8 CAR-positive viable T cells (non-weight based).

See the accompanying Lot information sheet (LIS) for additional information pertaining to dose.

Bridging therapy
Consider bridging therapy according to prescriber's choice prior to infusion with CARVYKTI to reduce tumour burden or stabilise the disease (see section 4.4).

Pre-treatment (lymphodepleting regimen)
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) (see section 5.1).
The availability of CARVYKTI should be confirmed prior to starting the lymphodepleting regimen.
A lymphodepleting regimen of cyclophosphamide 300 mg/m^2 intravenous and fludarabine 30 mg/m^2 intravenous should be administered daily for 3 days. CARVYKTI infusion should be administered 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, thereby 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 of cyclophosphamide and fludarabine, see corresponding Summaries of Product Characteristics of cyclophosphamide and fludarabine.

Premedication
The following pre-infusion medications should be administered to all patients 30 to 60 minutes prior to CARVYKTI infusion:
- Antipyretic (oral or intravenous paracetamol 650 to 1,000 mg).
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).

The use of prophylactic systemic corticosteroids should be avoided as it may interfere with the activity of CARVYKTI.

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

Patients seropositive for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV)
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 before collection of cells for manufacturing.

Paediatric population
The safety and efficacy of CARVYKTI in children aged below 18 years of age have not been established.
No data are available.

Method of administration
CARVYKTI is for intravenous use only.

Do NOT use a leukodepleting filter.

Preparation of CARVYKTI for infusion
Prior to infusion and during the recovery period, the availability of tocilizumab, or suitable alternatives, in the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, and emergency equipment must be ensured.

Before infusion, it must be confirmed that the patient's identity matches the unique patient information on the CARVYKTI cryo cassette, infusion bag and on the Lot Information Sheet. (see section 4.4).

The medicinal product must not be thawed until it is ready to be used. The timing of CARVYKTI thaw and infusion should be coordinated; the infusion time should be confirmed in advance, and the start time for thaw must be adjusted so that CARVYKTI is available for infusion when the patient is ready. The medicinal product should be administered immediately after thawing and the infusion should be completed within 2.5 hours of thawing.

For detailed instructions on preparation, administration, measures to take in case of accidental exposure and disposal of CARVYKTI, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance(s) 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

Traceability
The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability, the name of the medicinal product, the batch number and the name of the treated patient should be kept for a period of 30 years after the expiry date of the medicinal product.

General
Autologous use
CARVYKTI is intended solely for autologous use and must not, under any circumstances, be administered to other patients. CARVYKTI must not be infused if the information on the product labels and Lot Information Sheet does not match the patient's identity.

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 lymphodepletion regimen, 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.

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. There is no experience of use of CARVYKTI in patients with CNS involvement of myeloma or other pre-existing, clinically relevant CNS illnesses.
The efficacy/safety of CARVYKTI in patients previously exposed to other anti-BCMA treatments is unknown.
There is limited evidence available on efficacy/safety of CARVYKTI in re-treated patients.

Monitoring after infusion
Patients should be monitored daily for 14 days after the CARVYKTI infusion at a qualified clinical facility, and then periodically for an additional 2 weeks after CARVYKTI infusion, for signs and symptoms of CRS, neurologic events and other toxicities (see section 4.4).
Patients should be instructed to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion.

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*)*. The median time from CARVYKTI infusion (Day 1) to onset of CRS was 7 days (range: 1 to 12 days). Approximately 90% of patients experienced CRS onset after Day 3 of receiving the CARVYKTI infusion.

In almost all cases, duration of CRS ranged from 1 to 15 days (median duration, 4 days). Ninety percent of patients had 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 haemophagocytic lymphohistiocytosis (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.

The infusion of CARVYKTI should be delayed 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). 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.

The availability of at least one dose of tocilizumab for use in the event of CRS should be ensured prior to infusion. The qualified treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, the treatment centre must have access to suitable alternative measures instead of tocilizumab to treat CRS. Patients should be monitored for signs and symptoms of CRS daily for 14 days after the CARVYKTI infusion at a qualified clinical facility, and then periodically for an additional two weeks after CARVYKTI infusion.

Patients should be counselled to seek immediate medical attention should signs or symptoms of CRS occur at any time. At the first sign of CRS, the patient should be immediately evaluated for hospitalisation and treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids should be instituted as indicated in Table 1 below.

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 (see section 4.2).

Management of cytokine release syndrome associated with CARVYKTI
If CRS is suspected, manage according to the recommendations in Table 1. Supportive care for CRS (including but not limited to anti-pyretic agents, IV fluid support, vasopressors, supplemental oxygen, etc.) should be administered as appropriate. Laboratory testing to monitor for disseminated intravascular coagulation, haematology parameters, as well as pulmonary, cardiac, renal, and hepatic function should be considered. 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 HLH that remain 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 1: CRS grading and management guidance

<table>
<tr><th>CRS Grade[a]</th><th>Tocilizumab[b]</th><th>Corticosteroids[f]</th></tr>
<tr><td>Grade 1
Temperature ≥38 °C[c]</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>Grade 2
Symptoms require and respond to moderate intervention.

Temperature ≥38 °C[c] with:

Hypotension not requiring vasopressors,
and/or,</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>Hypoxia requiring oxygen via cannula[e] or blow-by,

or,

Grade 2 organ toxicity.</td><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>
</table>

<table>
<tr><td rowspan="2">Grade 3
Symptoms require and respond to aggressive intervention.

Temperature ≥38 °C[c] with:</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 haemodialysis (CVVHD).

Temperature ≥38 °C[c] with:</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 agents[d]. 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>
<tr><td colspan="3">Hypotension requiring one vasopressor with or without vasopressin,
and/or,

Hypoxia requiring oxygen via high-flow nasal cannula[e], facemask, non-rebreather mask, or Venturi mask,

or,

Grade 3 organ toxicity or Grade 4 transaminitis.</td></tr>
<tr><td colspan="3">Hypotension requiring multiple vasopressors (excluding vasopressin),
and/or,

Hypoxia requiring positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation),

or,

Grade 4 organ toxicity (excluding transaminitis).</td></tr>
</table>

[a] Based on ASTCT 2019 grading system (Lee et.al, 2019), modified to include organ toxicity.

[b] Refer to tocilizumab prescribing information for details. Consider alternative measures (see Sections 4.2. and 4.4).

[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 (for example, anti-IL1 such as anakinra) 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

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

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Patients receiving CARVYKTI may experience fatal or life-threatening ICANS following treatment with CARVYKTI, including before CRS onset, concurrent with CRS, following resolution of CRS or in the absence of CRS. Symptoms included aphasia, slow speech, dysgraphia, encephalopathy, depressed level of consciousness and confusional state.

Reduction of baseline burden of disease with bridging therapy prior to infusion with CARVYKTI in patients with high tumour burden should be considered, which may mitigate the risk of developing neurologic toxicity (see section 4.8). Patients should be monitored for signs or symptoms of ICANS for four weeks after infusion. At the first sign of ICANS, the patient should be immediately evaluated for hospitalisation and treatment instituted with supportive care as indicated in Table 2 below. Early detection and aggressive treatment of CRS or ICANS may be important to prevent neurologic toxicity from occurring or worsening. Continue to monitor patients for signs and symptoms of neurologic toxicities after recovery from CRS and/or ICANS.

Management of neurologic toxicity associated with CARVYKTI

At the first sign of neurologic toxicity including ICANS, neurology evaluation should be considered. Rule out other causes of neurologic symptoms. Provide intensive care and supportive therapy for severe or life-threatening neurologic toxicities.

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 Grade[a]	Corticosteroids
Grade 1 ICE score 7-9[b] or depressed level of consciousness: awakens spontaneously.	Consider dexamethasone[c] 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-3-6[b] or depressed level of consciousness: awakens to voice	Administer dexamethasone[c] 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-0-2[b] (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: • any clinical seizure, focal or generalised, that resolves rapidly, or • non-convulsive seizures on EEG that resolve with intervention, or raised intracranial pressure (ICP): focal/local oedema on neuroimaging[d].	Administer dexamethasone[c] 10 mg-20 mg intravenously every 6 hours. If no improvement after 48 hours or worsening of neurologic toxicity, escalate dexamethasone[c] 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.

Grade 4 ICE score-0[b] (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 findings[e]: • deep focal motor weakness such as hemiparesis or paraparesis, or raised ICP / cerebral oedema, with signs/symptoms such as: • diffuse cerebral oedema on neuroimaging, or • decerebrate or decorticate posturing, or • cranial nerve VI palsy, or • papilledema, or • Cushing's triad	Administer dexamethasone[c] 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 oedema 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.

EEG=Electroencephalogram; ICE=Immune Effector Cell-Associated Encephalopathy
Note: ICANS grade and management is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral oedema), 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 as in Table 3 below.

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

[d] Intracranial haemorrhage with or without associated oedema 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.

Table 3: Immune Effector Cell-Associated Encephalopathy (ICE) Assessment

Immune Effector Cell-Associated Encephalopathy (ICE) Tool[a]	
	Points
Orientation: Orientation to year, month, city, hospital	4
Naming: Name 3 objects (e.g., point to clock, pen, button)	3
Following commands: (e.g., 'Show me 2 fingers' or 'Close your eyes and stick out your tongue')	1
Writing: Ability to write a standard sentence	1
Attention: Count backwards from 100 by ten	1

[a] ICE-Tool Scoring:
- Score 10: No impairment
- Score 7-9: Grade 1 ICANS
- Score 3-6: Grade 2 ICANS

- Score 0-2: Grade 3 ICANS
- Score 0: patient unarousable and unable to perform ICE assessment: Grade 4 ICANS

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 at baseline (bone marrow plasma cell ≥80% or serum M-spike ≥ 5 g/dL or serum free light chain ≥ 5,000 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.

Patients should be monitored 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 section 4.8).

Patients should be monitored for GBS. Patients presenting with peripheral neuropathy should be evaluated for GBS. Treatment with intravenous immunoglobulin (IVIG) and escalation to plasmapheresis should be considered, depending on toxicity severity.

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

Patients should be monitored for signs and symptoms of peripheral neuropathies. Management with short-course systemic corticosteroids should be considered, 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.

Patients should be monitored for signs and symptoms of cranial nerve palsies. Management with short-course systemic corticosteroids should be considered, 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 or lower by Day 30 (see section 4.8).

Blood counts should be monitored prior to and after CARVYKTI infusion. For thrombocytopenia, supportive care with transfusions should be considered. 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).
Patients should be monitored for signs and symptoms of infection prior to and during treatment with CARVYKTI and treated appropriately. Prophylactic antimicrobials should be administered 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. Patients should be counselled 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 treated with medicinal products directed against B cells.

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 before collection of cells for manufacturing (see section 4.2).

Hypogammaglobulinaemia
Hypogammaglobulinaemia may occur in patients receiving CARVYKTI.

Immunoglobulin levels should be monitored after treatment with CARVYKTI; IVIG should be administered for IgG <400 mg/dL. Manage according to standard guidelines, including antibiotic or antiviral prophylaxis and monitoring for infection.

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. Patient should be monitored life-long for secondary malignancies. In the event a secondary malignancy occurs, the company should be contacted to obtain instructions on patient samples to collect for testing.

Interference with virological testing
Due to limited and short spans of identical genetic information between the lentiviral vector used to create CARVYKTI and HIV, some HIV nucleic acid tests (NAT) may give a false positive result.

Blood, organ, tissue and cell donation
Patients treated with CARVYKTI should not donate blood, organs, tissues and cells for transplantation. This information is provided in the Patient Alert Card which should be given to the patient.

Hypersensitivity
Allergic reactions may occur with infusion of CARVYKTI. Serious hypersensitivity reactions, including anaphylaxis, may occur 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.

Long-term follow-up
Patients are expected to enrol and be followed in a registry in order to better understand the long-term safety and efficacy of CARVYKTI.

4.5 Interaction with other medicinal products and other forms of interaction

No pharmacokinetic or pharmacodynamic drug interaction studies have been performed with CARVYKTI.

The co-administration of agents known to inhibit T cell function has not been formally studied. The co-administration of agents known to stimulate T cell function has not been investigated and the effects are unknown.

Some patients in the clinical trials on CARVYKTI 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).

Live vaccines
The safety of immunisation with live viral vaccines during or following CARVYKTI treatment has not been studied. As a precautionary measure, 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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females
Pregnancy status for females of childbearing potential 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.

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

Pregnancy
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 hypogammaglobulinaemia. Assessment of immunoglobulin levels in newborns of mothers treated with CARVYKTI should be considered.

Breast-feeding
It is unknown whether CARVYKTI is excreted in human milk. Women who are breast-feeding should be advised of the potential risk to the breast-fed infant.
Following administration of CARVYKTI, the decision to consider breast-feeding should be discussed with the treating physician.

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 (see section 5.3).

4.7 Effects on ability to drive and use machines

CARVYKTI has major influence on the 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 (see section 4.4). Patients should be advised 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 Undesirable effects

Summary of the safety profile
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) and an additional cohort (Japan; n=9), and Study MMY2003 (n=81).

The most common CARVYKTI adverse reactions (≥20%) were neutropenia (94%), CRS (89%), pyrexia (89%), thrombocytopenia (74%), anaemia (73%), leukopenia (55%), lymphopenia (46%), musculoskeletal pain (44%), hypotension (42%), fatigue (41%), transaminase elevation (37%), upper respiratory tract infection (35%), diarrhoea (30%), hypocalcaemia (27%), nausea (27%), headache (26%), cough (26%), hypophosphataemia (25%), encephalopathy (23%), oedema (23%), tachycardia (22%), chills (22%), decreased appetite (21%),and hypokalaemia (20%).

Serious adverse reactions occurred in 45% of patients; serious adverse reactions reported in ≥2% of patients were CRS (17%), sepsis (6%), ICANS (5%), encephalopathy (5%), neutropenia (5%), pneumonia (4%), febrile neutropenia (4%), bacterial infection (3%), upper respiratory tract infection (3%), HLH (3%), thrombocytopenia (3%), cranial nerve palsies (3%), renal failure (3%), leukopenia (2%), motor dysfunction (2%), neuropathy peripheral (2%), neurotoxicity (2%), cardiac arrhythmias (2%), dyspnoea (2%), hypoxia (2%).

The most common (≥5%) Grade ≥ 3 non-haematological adverse reactions were transaminase elevation (16%), Gamma-glutamyltransferase increased (8%), hypotension (7%), hypophosphataemia (7%), pneumonia (7%), sepsis (7%), pyrexia (6%), fatigue (6%), encephalopathy (5%), motor dysfunction (5%), hypocalcaemia (5%) and hypoxia (5%).

The most common (≥20%) Grade ≥3 haematological abnormalities were neutropenia (93%), anaemia (57%), leukopenia (54%), thrombocytopenia (51%) and lymphopenia (44%).

Tabulated list of adverse reactions
Table 4 summarises the adverse reactions that occurred in patients receiving CARVYKTI.
Within each system organ class, the adverse reactions are ranked by frequency. Within each frequency grouping, where relevant, adverse reactions are presented in order of decreasing seriousness. using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 4: Adverse reaction 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	Bacterial infection[*#]	11	4
		Upper respiratory tract infection[*]	35	3
	Common	Sepsis[1#]	9	7
		Pneumonia[*#]	9	8
		Viral infection[*]	5	2
		Fungal infection[*]	3	1
		Cytomegalovirus infection[*]	2	2
Blood and lymphatic system disorders	Very common	Neutropenia[*]	94	93
		Thrombocytopenia	74	51
		Anaemia	73	57
		Leukopenia	55	54
		Lymphopenia	46	44
		Febrile neutropenia	13	12
		Coagulopathy[2]	15	2
		Hypofibrinogenaemia[*]	12	3
Immune system disorders	Very common	Hypogammaglobulinaemia[*]	12	1
		Cytokine release syndrome[#]	89	4
	Common	Haemophagocytic lymphohistiocytosis[#]	3	2
Metabolism and nutrition disorders	Very common	Hypocalcaemia	27	5
		Hypophosphataemia	25	7
		Decreased appetite	21	2
		Hypokalaemia	20	3
		Hypoalbuminaemia	18	1
		Hyponatraemia	19	4
		Hypomagnesaemia	16	0
Psychiatric disorders	Common	Delirium[3]	5	1
		Personality changes[4]	4	1
		Insomnia	9	0
Nervous system disorders	Very common	Encephalopathy[5]	24	5
		Immune effector cell-associated neurotoxicity syndrome[#]	16	3
		Motor dysfunction[6]	17	5
		Neuropathy peripheral[7]	13	3
		Dizziness[*]	17	1
		Headache	26	0
	Common	Aphasia[8]	7	1
		Guillain-Barre syndrome	1	1
		Cranial nerve palsies[9]	5	1
		Paresis[10]	2	1
		Ataxia[11]	6	1
		Tremor[*]	6	1
		Neurotoxicity[#]	2	2
Cardiac disorders	Very common	Tachycardia[*]	22	1
	Common	Cardiac arrhythmias[12]	6	2
Vascular disorders	Very common	Hypotension[*]	42	7

		Hypertension	15	4
	Common	Haemorrhage[13#]	8	2
		Thrombosis[*]	6	1
Respiratory, thoracic and mediastinal disorders	Very common	Hypoxia[*]	13	5
		Dyspnoea[14#]	19	4
		Cough[*]	26	0
Gastrointestinal disorders	Very common	Diarrhoea	30	2
		Nausea	27	1
		Vomiting	18	0
		Constipation	18	0
		Abdominal pain[*]	10	0
Hepatobiliary disorders	Common	Hyperbilirubinaemia	5	2
Skin and subcutaneous tissue disorders	Common	Rash[*]	9	0
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain[*]	44	4
Renal and urinary disorders	Common	Renal failure[15]	7	4
General disorders and administration site conditions	Very common	Pyrexia	89	6
		Fatigue[*]	41	6
		Chills	22	0
		Oedema[16]	23	2
		Pain[*]	13	1
Investigations	Very common	Transaminase elevation[*]	37	16
		Gamma-glutamyltransferase increased	14	8
		Serum ferritin increased	12	3
		Blood lactate dehydrogenase increased	11	0
		Blood alkaline phosphatase increased	11	3
	Common	C-reactive protein increased	8	2

Adverse reactions are reported using MedDRA version 24.1

[#] Contains fatal outcome(s).

[*] Based on grouped term.

[1] Sepsis includes bacteraemia, bacterial sepsis, enterococcal bacteraemia, pseudomonal bacteraemia, sepsis, septic shock, staphylococcal bacteraemia and streptococcal sepsis.

[2] 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.

[3] Delirium includes agitation, delirium, euphoric mood, hallucination, irritability, and restlessness.

[4] Personality changes includes apathy, flat affect, indifference, personality change, and reduced facial expression.

[5] Encephalopathy includes amnesia, bradyphrenia, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, encephalopathy, hypersomnia, lethargy, memory impairment, mental impairment, mental status changes, psychomotor retardation, sleep disorder, and somnolence.

[6] 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.

[7] Neuropathy peripheral includes hypoaesthesia, neuralgia, paraesthesia, paraesthesia ear, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy, and sensory loss.

[8] Aphasia includes aphasia, dysarthria, slow speech, and speech disorder.

[9] Cranial nerve palsies include Bell`s palsy, cranial nerve paralysis, facial nerve disorder, facial paralysis, facial paresis, and VIth nerve paralysis.

[10] Paresis includes hemiparesis, paresis, and peroneal nerve palsy.

[11] Ataxia includes ataxia, balance disorder, and gait disturbance.

[12] Cardiac arrhythmias include atrial fibrillation, atrial flutter, supraventricular tachycardia, ventricular extrasystoles, and ventricular tachycardia.

[13] Haemorrhage includes conjunctival haemorrhage, epistaxis, haemoptysis, post procedural haemorrhage, pulmonary haemorrhage, retinal haemorrhage, and subarachnoid haemorrhage.

[14] Dyspnoea includes acute respiratory failure, dyspnoea, dyspnoea exertional, respiratory failure, and wheezing.

[15] Renal failure includes acute kidney injury, blood creatinine increased, and chronic kidney disease.

[16] Oedema includes face oedema, fluid retention, generalised oedema, hypervolaemia, joint swelling, localised oedema, oedema, oedema peripheral, palatal oedema, periorbital oedema, peripheral swelling, pulmonary congestion, pulmonary oedema, and scrotal oedema.

Description of selected adverse reactions

Cytokine release syndrome

CRS was reported in 89% of patients (n=166); 84% (n=157) of patients had CRS events that were Grade 1 or Grade 2, 4% (n=8) of patients had Grade 3 or Grade 4 CRS events and <1% (n=1) of patients had a Grade 5 CRS event. Ninety-eight percent of patients (n=163) recovered from CRS. The duration of CRS was ≤15 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 (86%), hypotension (35%), Aspartate aminotransferase (AST) increased (18%), and Alanine aminotransferase (ALT) increased (13%). See section 4.4 for monitoring and management guidance.

Neurologic toxicities

Neurologic toxicity occurred in 23% of patients (n=42); 7% (n=14) of patients had Grade 3 or Grade 4 neurologic toxicity and 2% (n=3) of patients had Grade 5 neurologic toxicity (one due to ICANS, one due to neurologic toxicity with ongoing parkinsonism, and one due to encephalopathy). In addition, six patients had fatal outcomes with ongoing neurologic toxicity at the time of death; five deaths were due to infection, including two deaths in patients with ongoing signs and symptoms of parkinsonism, as discussed below, and one death was due to respiratory failure. See section 4.4 for monitoring and management guidance.

Immune effector cell-associated neurotoxicity syndrome (ICANS)

In the pooled studies (n=187), ICANS occurred in 16% of patients (n=29), with 3% (n=5) experiencing Grade 3 or 4 ICANS and <1% (n=1) Grade 5 ICANS. Symptoms included aphasia, slow speech, dysgraphia, encephalopathy, depressed level of consciousness and confusional state. The median time from CARVYKTI infusion to first onset of ICANS was 8 days (range: 2 to 13 days,

except for 1 patient with onset at 26 days) and the median duration was 4 days (range: 1 to 29 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 42 patients in the pooled studies (n=187) experiencing any neurotoxicity, seven 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), Grade 3 (n=6). The median onset of parkinsonism was 38.0 days (range: 14 to 914 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. One patient recovered (Grade 3). The remaining 3 patients (Grade 3), symptoms of parkinsonism were ongoing up to 996 days after administration of CARVYKTI. All 7 patients had a history of prior CRS (n=5 Grade 2; n=1 Grade 3; n=1 Grade 4), while 4 of 7 patients had prior ICANS (n=4 Grade 1).

Guillain-Barré syndrome
In the pooled studies (n=187), 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 the pooled studies (n=187), 13 patients developed peripheral neuropathy, presenting as sensory, motor, or sensorimotor neuropathies. Median time of onset of symptoms was 66 days (range: 4 to 914 days), median duration of peripheral neuropathies was 138 days (range: 2 to 692 days) including those with ongoing neuropathy. Of these 13 patients, 4 experienced Grade 3 or Grade 4 peripheral neuropathy (which resolved in 2 patients either with no treatment reported or following intervention including duloxetine, metamizole, prednisone and pregabalin, and was ongoing in the other 2 patients, including one patient who improved after treatment with dexamethasone); of the remaining 9 with ≤ Grade 2 peripheral neuropathy, peripheral neuropathy resolved with no treatment reported in 2 patients and following treatment with duloxetine in 1 patient, and was ongoing in the other 6 patients.

Cranial nerve palsies
In the pooled studies (n=187), 10 patients experienced cranial nerve palsies. Median time to onset was 24 days (range: 20 to 101 days) following infusion of CARVYKTI, and median time to resolution was 51 days (range: 1 to 128 days) following onset of symptoms.

Prolonged and recurrent cytopenias
Grade 3 or 4 cytopenias at Day 1 after dosing, not resolved to Grade 2 or lower by Day 30 following CARVYKTI infusion, included, thrombocytopenia (36%), neutropenia (31%), and lymphopenia (21%). After Day 60 following CARVYKTI, 28%, 17%, and 3% of patients had an occurrence of Grade 3 or 4 lymphopenia, neutropenia, and thrombocytopenia respectively, after initial recovery of their Grade 3 or 4 cytopenia.

Table 5 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.

Table 5: Incidences of prolonged and recurrent cytopenias following treatment with CARVYKTI (N=187)

	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	99 (53%)	68 (36%)	44 (24%)	6 (3%)
Neutropenia	180 (96%)	58 (31%)	22 (12%)	31 (17%)
Lymphopenia	183 (98%)	39 (21%)	22 (12%)	52 (28%)

[a] The laboratory result with the worst toxicity grade is 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 < 50,000 cells/µL.
Neutropenia: Grade 3/4 - Neutrophil count < 1,000 cells/µL.
Lymphopenia: Grade 3/4 - Lymphocytes count < 0.5×10^9 cells/L.
Percentages are based on the number of treated patients.

Serious infections
Infections occurred in 48% of patients (n=89); 16% of patients (n=29) experienced Grade 3 or Grade 4 infections, and fatal infections occurred in 3% of patients (n=5)- lung abscess, sepsis, septic shock, COVID-19 pneumonia and *Clostridium difficile* colitis. The most frequently reported (≥ 2%) 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 for monitoring and management guidance.

Hypogammaglobulinaemia
In the pooled studies (n=187), hypogammaglobulinaemia occurred in 11% of patients, with 1% of patients experiencing Grade 3 hypogammaglobulinaemia. Laboratory IgG levels fell below 500 mg/dL after infusion in 88% (165/187) of patients treated with CARVYKTI. Hypogammaglobulinaemia either as an adverse reaction or a laboratory IgG level below 500 mg/dL occurred in 90% (168/187) of patients after infusion. Thirty-six percent of patients received IVIG post CARVYKTI for either an adverse reaction or prophylaxis. See section 4.4 for monitoring and management guidance.

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 the pooled studies (N=187), 46 of 187 (25%) patients with appropriate samples were positive for treatment-emergent anti-CAR antibodies. There was no clear evidence that the observed anti-CAR antibodies had an impact on the safety of CARVYKTI.
Further, analysis in Study MMY2001 (n=97) showed no clear evidence to suggest that the observed anti-CAR antibodies impact CARVYKTI kinetics of initial expansion and persistence, efficacy or safety.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

There are no data regarding the signs or sequelae of overdose with CARVYKTI.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: L01XL05

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) signaling cytoplasmic domain. Upon binding to BCMA expressing cells, the CAR promotes T cell activation, expansion, and elimination of target cells.

Pharmacodynamic effects
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.

Clinical efficacy and safety
MMY2001 was an open label, single-arm, multicentre, Phase 1b/2 study evaluating the efficacy and safety of CARVYKTI for the treatment of adult patients with relapsed and refractory multiple myeloma who had received at least 3 prior lines of antimyeloma therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and who had disease progression on or within 12 months after the last regimen. Patients with known active, or prior history of significant central nervous system (CNS) disease including CNS multiple myeloma, patients previously exposed to other anti-BCMA treatments, allogeneic 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.

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 medicinal 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 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 (63.9%), bortezomib: 26 patients (26.8%), cyclophosphamide: 22 patients (22.7%), and pomalidomide: 21 patients (21.6%).

CARVYKTI was administered as a single IV infusion 5 to 7 days after the start of a lymphodepleting chemotherapy (cyclophosphamide 300 mg/m^2 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 hospitalised for the 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).

Table 6: Summary of patient demographic and baseline characteristics

Analysis set	All Treated (N=97)	All Leukapheresed (N=113)
Age (years)		
Category n (%)		
< 65	62 (64)	70 (62)
65 – 75	27 (28)	34 (30)
> 75	8 (8)	9 (8)
Median (range)	61.0 (43; 78)	62 (29; 78)
Sex		
Male n (%)	57 (59)	65 (57.5)
Female n (%)	40 (41)	48 (42.5)
Race		
American Indian or Alaska native	1 (1)	1 (1)
Asian	1 (1)	1 (1)
Black or African American	17 (17.5)	17 (15)
Native Hawaiian or other Pacific islander	1 (1)	1 (1)
White	69 (71)	83 (73.5)
Multiple	0	0
Not reported	8 (8)	10 (9)
ECOG score prior to infusion n (%)		
0	39 (40)	55 (49)
1	54 (56)	58 (51)
2	4 (4)	-
ISS staging at study baseline n (%)		
N	97	58
I	61 (63)	32 (55)
II	22 (23)	21 (36)
III	14 (14)	5 (9)
Creatinine Clearance/eGFR (MDRD) (mL/min/1.73m^2) Median (range)	88.44 (41.8, 242.9)	73.61 (36.2, 177.8)
Time since initial multiple myeloma diagnosis to enrollment (years) Median (range)	5.94 (1.6; 18.2)	5.73 (1.0; 18.2)
Presence of extramedullary plasmacytomas n (%)		
Yes	13 (13)	NA[a]
No	84 (87)	NA[a]
Cytogenetic risk at study baseline n (%)		
Standard risk	68 (70)	70 (62)
High risk	23 (24)	28 (25)
Del17p	19 (20)	22 (19.5)
T(4;14)	3 (3)	5 (4)
T(14;16)	2 (2)	3 (3)
Unknown	6 (6)	15 (13)
Tumour BCMA expression (%) Median (range)	80 (20; 98)	80 (20; 98)
Number of lines of prior therapies for multiple myeloma Median (range)	6 (3,18)	5 (3, 18)
Prior treatment with PI+IMiD+anti-CD38 antibodies n (%)	97 (100)	113 (100)
Prior autologous SCT n (%)	87 (90)	99 (88)
Prior allogeneic SCT n (%)	8 (8)	8 (7)
Refractory at any point to prior therapy n (%)	97 (100)	113 (100)
Refractory to PI+IMiD+anti-CD38 antibody n (%)	85 (88)	100 (88.5)

Refractory to last line of prior therapy n (%)	96 (99)	112 (99)

ECOG= Eastern Cooperative Oncology Group; ISS= International Staging System; PI= Proteasome inhibitor; IMiD= Immunomodulatory drug; SCT= Stem cell transplant; NA= not applicable.

[a] Plasmacytomas were not assessed until prior to lymphodepletion.

Efficacy results were based on overall response rate as determined by the Independent Review Committee assessment using IMWG criteria (see Table 7).

Table 7: Efficacy results for Study MMY2001

Analysis set	**All Treated (N=97)**	**All Leukapheresed (N=113)**
Overall Response Rate (sCR[a] + VGPR + PR) n (%) 95% CI (%)	95 (97.9) (92.7, 99.7)	95 (84.1) (76.0, 90.3)
Stringent complete response (sCR)[a] n (%)	80 (82.5)	80 (70.8)
Very good partial response (VGPR) n (%)	12 (12.4)	12 (10.6)
Partial response (PR) n (%)	3 (3.1)	3 (2.7)
Duration of Response (DOR) (months)[b] Median (95% CI)	 NE (28.3, NE)	-
DOR if best response is sCR[a] (months) Median (95% CI)	 NE (28.3, NE)	-
Time to Response (months) Median (Range)	 0.95 (0.9; 10.7)	 -
MRD negativity rate n (%)[c] 95% CI (%)	56 (57.7) (47.3, 67.7)	56 (49.6) (40.0, 59.1)
MRD negative patients with sCR n (%)[c] 95% CI (%)	42 (43.3) (33.3, 53.7)	42 (37.2) (28.3, 46.8)

CI=confidence interval; MRD= Minimal Residual Disease; NE= not estimable

Notes: Based on a median duration of follow up of 28 months

[a] All complete responses were stringent CRs.

[b] The estimated DOR rate was 60.3% (95% CI: 49.6%, 69.5%) at 24 months and 51.2% (95% CI: 39.0%, 62.1%) at 30 months.

[c] 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. MRD negativity rate [(%) 95% CI] in evaluable patients (n=61) was 91.8% (81.9%, 97.3%).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with CARVYKTI in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called 'conditional approval' scheme.
This means that further evidence on this medicinal product is awaited.
The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

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 8: 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	1098030 (1387010), 97
$AUC_{0\text{-}6m}$ (copies*day/µg genomic DNA)	Mean (SD), n	1033373 (1355394), 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 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: 28-365 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.

Special populations
The pharmacokinetics of CARVYKTI (C_{max} and $AUC_{0\text{-}28d}$) were not impacted by age (range: 43-78 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 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

CARVYKTI comprises engineered human T cells; therefore, there are no representative *in vitro* assays, *ex vivo* models, or *in vivo* models that can accurately address the toxicological characteristics of the human product. Hence, traditional toxicology studies used for medicinal product development were not performed.

Carcinogenicity and mutagenicity
No genotoxicity or carcinogenicity studies have been performed.

The risk for insertional mutagenesis occurring during the manufacturing of CARVYKTI 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 samples from 6 multiple myeloma patients and from 3 samples from 3 healthy donors. There was no evidence for preferential integration near genes of concern.

Reproductive toxicology
No reproductive and developmental toxicity animal studies have been conducted with CARVYKTI.

No studies have been conducted to evaluate the effects of CARVYKTI on fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cryostor CS5 (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

9 months.

Once thawed: maximum 2.5 hours at room temperature (20 °C to 25 °C). CARVYKTI infusion must be administered immediately after thawing and completed within 2.5 hours.

6.4 Special precautions for storage

CARVYKTI must be stored and transported in the vapour phase of liquid nitrogen (≤ -120 °C) and must remain frozen until the patient is ready for treatment to ensure viable cells are available for patient administration.
Thawed medicinal product must not be shaken, refrozen or refrigerated.

Keep infusion bag in the aluminium cryo cassette.
For storage conditions after thawing of the medicinal product, see section 6.3.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Ethylene vinyl acetate (EVA) infusion bag with sealed addition tube and two available spike ports containing either 30 mL (50 mL bag) or 70 mL (250 mL bag) of cell dispersion.
Each infusion bag is packed in an aluminium cryo cassette.

6.6 Special precautions for disposal and other handling

CARVYKTI should not be irradiated as irradiation could inactivate the medicinal product.

Precautions to be taken before handling or administering the medicinal product
CARVYKTI should be transported within the facility in closed, break-proof and leak-proof containers.

This medicinal product contains human blood cells. Healthcare professionals handling CARVYKTI should take appropriate precautions (wearing gloves, protective clothing and eye protection) to avoid potential transmission of infectious diseases.
CARVYKTI must remain ≤ -120 °C at all times, until the content of the bag is thawed for infusion.

Preparation prior to administration
The timing of CARVYKTI thaw and infusion should be coordinated; the infusion time should be confirmed in advance, and the start time for thaw must be adjusted so that CARVYKTI is available for infusion when the patient is ready. Once thawed, the medicinal product should be administered immediately and the infusion should be completed within 2.5 hours.

- Prior to CARVYKTI preparation, patient identity should be confirmed by matching the patient's identity with the patient identifiers on the CARVYKTI cryo cassette and Lot Information Sheet. The CARVYKTI infusion bag should not be removed from the cryo cassette if the information on the patient-specific label does not match the intended patient.
- Once patient identification is confirmed, the CARVYKTI infusion bag should be removed from the cryo cassette.
- The infusion bag should be inspected for any breaches of container integrity such as breaks or cracks before and after thawing. Do not administer if the bag is compromised and contact **Janssen-Cilag International NV**.

Thawing
- The infusion bag should be placed inside a sealable plastic bag prior to thawing.
- CARVYKTI should be thawed at 37 °C±2 °C using either a water bath or dry thaw device 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.
- The infusion bag should be removed from the sealable plastic bag and wiped dry. The contents of the infusion bag should be gently mixed to disperse clumps of cellular material. If visible cell clumps remain, the contents of the bag should continue to be gently mixed. Small clumps of cellular material should disperse with gentle manual mixing. CARVYKTI must not be pre-filtered into a different container, washed, spun down, and/or resuspended in new media prior to infusion.
- Once thawed, the medicinal product should not be re-frozen or refrigerated.

Administration
- CARVYKTI is for autologous single use only.
- Prior to infusion and during the recovery period, ensure tocilizumab and emergency equipment are available for use.
- Confirm the patient's identity with the patient identifiers on the CARVYKTI infusion bag and Lot Information Sheet. Do not infuse CARVYKTI if the information on the patient-specific label does not match the intended patient.
- Once thawed, the entire contents of the CARVYKTI bag should be administered by intravenous infusion within 2.5 hours at room temperature (20 °C to 25 °C), using infusion sets fitted with an in-line filter. The infusion usually takes less than 60 minutes.
- 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 for injection to ensure all medicinal product is delivered.

Precautions to be taken for the disposal of the medicinal product
Unused medicinal product and 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 guidelines on handling of human-derived material.

Measures to take in case of accidental exposure
In case of accidental exposure local guidelines on handling of human-derived material should be followed. Work surfaces and materials which have potentially been in contact with CARVYKTI must be decontaminated with appropriate disinfectant.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1648/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 May 2022
Date of latest renewal: 24 March 2023

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Janssen Pharmaceuticals Inc.
1000 U.S. Route 202 South
Raritan, NJ, USA 08869

Name and address of the manufacturer(s) responsible for batch release

Janssen Biologics B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile, or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Controlled distribution program and availability of tocilizumab

To minimise the risks of CRS (including HLH) and neurotoxicity (including ICANS and other neurotoxicity) associated with the treatment of CARVYKTI the MAH will ensure that centres that dispense CARVYKTI are qualified in accordance with the agreed controlled distribution program by:

- ensuring immediate, on-site access to one dose of tocilizumab per patient prior to CARVYKTI infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, the MAH will ensure that suitable alternative measures to treat CRS instead of tocilizumab are available on-site.

CARVYKTI will only be supplied to centres that are qualified and only if the Healthcare professional (HCP) involved in the treatment of a patient has completed the HCP educational program.

Educational program: Prior to the launch of CARVYKTI in each Member State the MAH must agree the content and format of the educational materials with the National Competent Authority.

HCP educational program

The MAH shall ensure that in each Member State where CARVYKTI is marketed, all HCPs who are expected to prescribe, dispense, and administer CARVYKTI shall be provided with guidance:
- to increase awareness of CRS (including HLH) and neurotoxicity (including ICANS and other neurotoxicity) and its appropriate monitoring, prevention, and management, including the importance of on-site availability of tocilizumab before treating a patient.
- to facilitate patient counseling relevant information.
- on reporting these serious adverse reactions associated with CARVYKTI.
- before treating a patient, to ensure that tocilizumab for each patient is available on site; in the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensure that suitable alternative measures to treat CRS are available on site

Medicinal product handling training

The MAH shall ensure that all HCPs and other personnel involved in the transport, storage, thawing, preparation, or handling of CARVYKTI shall be provided training:
- to increase awareness of the important potential risk of decrease in cell viability due to inappropriate handling or preparation of the medicinal product.
- to provide guidance on precautions to take before handling or administering CARVYKTI (i.e., how to check the medicinal product prior to administration, how to thaw, and how to administer).

Patient educational program

To inform and explain to patients:
- the risks of CRS (including HLH) and neurotoxicity (including ICANS and other neurotoxicity) associated with CARVYKTI and increase awareness of symptoms requiring immediate medical attention.
- the need to carry the patient alert card at all times and share it with any HCP providing care (including emergency) so the HCP can contact the CAR-T treating HCP.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to further characterise the long-term safety and efficacy of CARVYKTI in adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and have demonstrated disease progression on the last therapy the MAH shall submit the results of the long-term follow-up study for participants previously treated with ciltacabtagene autoleucel.	June 2043
In order to further characterise the long-term safety of CARVYKTI in adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and have demonstrated disease progression on the last therapy the MAH shall conduct and submit the results of an observational post-authorisation safety study based on a registry.	December 2042
In order to further characterise the long-term safety of CARVYKTI in adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and have demonstrated disease progression on the last therapy the MAH shall conduct and submit the results of an observational post-authorisation safety study based on patient's data primarily from the EU region.	December 2042

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of CARVYKTI in adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and have demonstrated disease progression on the last therapy, the MAH should submit the results of the Phase 3 study CARTITUDE-4 (MMY3002).	December 2026

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CONTAINER (CRYO CASSETTE)

1. NAME OF THE MEDICINAL PRODUCT

CARVYKTI $3.2 \times 10^6 – 1 \times 10^8$ cells dispersion for infusion
ciltacabtagene autoleucel (CAR+ viable T cells)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

This medicine contains cells of human origin.

Autologous human T cells genetically modified *ex vivo* using a lentiviral vector encoding an anti-BCMA chimeric antigen receptor (CAR).

3. LIST OF EXCIPIENTS

Cryostor CS5 (contains dimethyl sulfoxide).

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion
30 mL or 70 mL of cell dispersion per bag.
See Lot information sheet.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not irradiate.
Do NOT use leukocyte depleting filter.
Do not shake.
Do not refrigerate.
Properly identify intended recipient and product.

Read the package leaflet before use.
Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For autologous use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport frozen ≤ -120 °C in vapour phase of liquid nitrogen.
Do not thaw the medicinal product until use.
Do not refreeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human blood cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1648/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot
Patient Name:
Patient DOB:
SEC:
Bag ID:
Order ID:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

INFUSION BAG

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

CARVYKTI $3.2 \times 10^6 – 1 \times 10^8$ cells dispersion for infusion
ciltacabtagene autoleucel (CAR+ viable T cells)
For intravenous use only.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot
Patient Name:
Patient DOB:
SEC:
Bag ID:
Order ID:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 mL or 70 mL of cell dispersion per bag
See Lot information sheet.

6. OTHER

For autologous use only.
Verify Patient ID

PARTICULARS TO APPEAR ON THE LOT INFORMATION SHEET INCLUDED WITH EACH SHIPMENT FOR ONE PATIENT

1. NAME OF THE MEDICINAL PRODUCT

CARVYKTI $3.2 \times 10^6 – 1 \times 10^8$ cells dispersion for infusion
ciltacabtagene autoleucel (CAR+ viable T cells)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Autologous human T cells genetically modified *ex vivo* using a lentiviral vector encoding an anti-BCMA chimeric antigen receptor (CAR).
This medicine contains cells of human origin.

3. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Lot number	Bag ID	Patient Weight (kg)	Total Volume (mL)	Product dose per bag

One aluminium cryo cassette containing one individually packed sterile infusion bag.

4. DOSE OF THE MEDICINAL PRODUCT

The target dose is 0.75×10^6 CAR-positive viable T cells/kg of body weight (not exceeding 1×10^8 CAR-positive viable T cells).

Patients 100 kg and below: $0.5 - 1 \times 10^6$ CAR-positive viable T cells/kg body weight.
Patients above 100 kg: $0.5 - 1 \times 10^8$ CAR-positive viable T cells (non-weight based).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.

6. OTHER SPECIAL WARNING(S), IF NECESSARY

SAVE THIS DOCUMENT AND HAVE IT AVAILABLE WHEN PREPARING FOR ADMINISTRATION OF CARVYKTI
For autologous use only.
Do not irradiate.
Do NOT use a leukodepletion filter.
Do not shake.
Do not refrigerate.
Properly identify intended recipient and product.

7. SPECIAL STORAGE CONDITIONS

Store and transport frozen (≤ -120 °C). Keep infusion bag in the aluminium cryo cassette until ready for thaw and administration. Place the infusion bag inside a sealable plastic bag prior to thawing. Do not unseal the bag until after thaw. Once thawed do not re-freeze.

8. EXPIRY DATE AND OTHER BATCH SPECIFIC INFORMATION

Manufactured by:	
Manufacture date:	
Expiration date:	DD/MMM/YYYY

9. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human blood cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

10. DONATION AND PRODUCT CODES

PATIENT INFORMATION
Patient Name:
Patient DOB:
SEC:
Order ID:

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1648/001

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

CARVYKTI 3.2 × 10^6 – 1 × 10^8 cells dispersion for infusion
ciltacabtagene autoleucel (CAR+ viable T cells)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- The doctor or nurse will give you a Patient Alert Card which contains important safety information about the treatment with CARVYKTI. Read it carefully and follow the instructions on it.
- Carry the Patient Alert Card with you at all times and always show it to any doctor or nurse who sees you or if you go to the hospital.

What is in this leaflet

1. What CARVYKTI is and what it is used for

- CARVYKTI is a type of medicine called a "genetically modified cell therapy" which is made especially for you from your own white blood cells, called T cells.
- CARVYKTI is used to treat adult patients with cancer of the bone marrow called multiple myeloma. It is given when at least three other kinds of treatment have not worked.

How CARVYKTI works
- The white blood cells taken from your blood are modified in the laboratory to insert a gene that allows them to make a protein called chimeric antigen receptor (CAR).
- The CAR can attach to a specific protein on the surface of myeloma cells allowing your white blood cells to recognise and attack the myeloma cells.

2. What you need to know before you are given CARVYKTI

You must not be given CARVYKTI
- if you are allergic to any of the ingredients of this medicine (listed in section 6).
- if you are allergic to any of the ingredients in the medicines you will be given to reduce the number of white blood cells in your blood (lymphodepleting therapy) before treatment with CARVYKTI (see also section 3, How CARVYKTI is given).

If you think you may be allergic, ask your doctor for advice.

Warnings and precautions
Tell your doctor before you are given CARVYKTI if you have:

- current or past problems with your nervous system - such as fits, stroke, new or worsening memory loss
- any lung, heart or blood pressure (low or raised) problems
- liver or kidney problems.
- signs or symptoms of graft-versus-host disease. This happens when transplanted cells attack your body, causing symptoms such as rash, nausea, vomiting, diarrhoea and bloody stools.

If any of the above apply to you (or you are not sure), talk to your doctor before you are given CARVYKTI.

Tests and checks
Before you are given CARVYKTI your doctor will:
- check the levels of blood cells in your blood
- check your lungs, heart and blood pressure
- look for signs of infection - an infection will be treated before you have CARVYKTI
- check if your cancer is getting worse
- check for hepatitis B, hepatitis C or HIV infection
- check if you had a vaccination in the last 6 weeks or plan to have one in the next few months.

After treatment with CARVYKTI your doctor will:
- regularly check your blood, as the number of blood cells and other blood components may decrease.

Tell your doctor right away if you get a fever, chills or any signs or symptoms of an infection, are feeling tired, or have bruising or bleeding.

Look out for serious side effects
There are serious side effects which you need to tell your doctor or nurse about straight away and which may require you to get immediate medical attention. See section 4 under ‘Serious side effects’.

Children and adolescents
CARVYKTI should not be used in children and adolescents below 18 years of age as the medicine has not been studied in this age group and it is not known if it is safe and effective.

Other medicines and CARVYKTI
Before you are given CARVYKTI tell your doctor or nurse if you are taking, have recently taken, or might take any other medicines.
In particular, tell your doctor or nurse if you are taking:
- medicines that weaken your immune system such as corticosteroids.

These medicines may interfere with the effect of CARVYKTI.

Vaccines and CARVYKTI
You must not be given certain vaccines called live vaccines:
- in the 6 weeks before you are given the short course of chemotherapy (called lymphodepleting chemotherapy) to prepare your body for the CARVYKTI cells.
- after CARVYKTI treatment while your immune system is recovering.

Talk to your doctor if you need to have any vaccinations.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before being given this medicine.
- This is because the effects of CARVYKTI in pregnant or breast-feeding women are not known.
- CARVYKTI may harm your unborn baby or your breast-fed child.

If you are pregnant or think you may be pregnant after treatment with CARVYKTI, talk to your doctor immediately.

You have to do a pregnancy test before treatment starts. CARVYKTI should only be given if the results show you are not pregnant.

If you have had CARVYKTI treatment, you should discuss any plans to have future pregnancies with your doctor.

Driving and using tools or machines
CARVYKTI can severely affect your ability to drive or use tools or machines causing side effects that may make you:
- feel tired
- have balance and coordination problems
- feel confused, weak or dizzy.

Do not drive or use tools or machines until at least 8 weeks after having CARVYKTI and if these symptoms return.

CARVYKTI contains dimethyl sulfoxide (DMSO) and kanamycin
This medicine contains DMSO (a substance used to preserve frozen cells) and may contain traces of kanamycin (an aminoglycoside antibiotic), both of which can sometimes cause allergic reactions. Your doctor will monitor you for any signs of a possible allergic reaction.

3. How CARVYKTI is given

CARVYKTI will always be given to you by a healthcare professional at a qualified treatment centre.

Making CARVYKTI from your own blood cells
CARVYKTI is made from your own white blood cells. Your blood cells will be collected from you to prepare your medicine.
- Your doctor will take some of your blood using a catheter (tube) placed in your vein.
- Some of your white blood cells are separated from your blood - the rest of your blood is returned to your vein. This process is called 'leukapheresis'.
- This process can take 3 to 6 hours and may need to be repeated.
- Your white blood cells are sent to the manufacturing centre where they are modified to make CARVYKTI. This process takes about 4 weeks.
- While CARVYKTI is made you may get other medicines to treat the multiple myeloma. This is so it does not get worse.

Medicines given before CARVYKTI treatment

A few days before - you will be given treatment called "lymphodepleting therapy" to prepare your body to receive CARVYKTI. This treatment reduces the number of white blood cells in your blood, so the genetically modified white blood cells in CARVYKTI can grow in numbers when they are returned to your body.

30 to 60 minutes before - you may be given other medicines. These may include:
- Antihistamine medicines for an allergic reaction - such as diphenhydramine
- medicines for fever - such as paracetamol.

Your doctor or nurse will check carefully that the CARVYKTI treatment you are given is from your own white blood cells.

How you are given CARVYKTI
CARVYKTI is a one-time treatment. It will not be given to you again.

- Your doctor or nurse will give you CARVYKTI by a drip into your vein. This is called an 'intravenous infusion' and is usually less than 60 minutes.

CARVYKTI is the genetically modified version of your white blood cells.

- Your healthcare professional handling CARVYKTI will take appropriate precautions to prevent the chance of transfer of infectious diseases.
- They will also follow local guidelines to clean up or dispose of any material that has been in contact with CARVYKTI.

After you are given CARVYKTI
- Plan to stay near the hospital where you were treated for at least 4 weeks after you are given CARVYKTI.
  - You will need to return to the hospital every day for at least 14 days after you are given CARVYKTI. This is so your doctor can check if your treatment is working and treat you if you get any side effects. If you do develop serious side effects, you may need to stay in the hospital until your side effects are under control and it is safe for you to leave.
  - If you miss any appointments, call your doctor or qualified treatment centre as soon as possible to make a new appointment.
- You will be asked to enrol in a registry for at least 15 years in order to monitor your health and better understand the long-term effects of CARVYKTI.
- Having CARVYKTI in your blood may cause some commercial HIV tests to incorrectly give you a HIV positive result even though you may be HIV negative.
- Do not donate blood, organs, tissues or cells for transplants after you have had CARVYKTI.

4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. CARVYKTI can cause side effects that may be serious or life-threatening.

Serious side effects
Get medical help straight away if you get any of the following serious side effects which may be severe and can be fatal.

- A serious immune reaction known as 'cytokine release syndrome (CRS)', some signs include:

  Very common (may affect more than 1 in 10 people):
  - chills, fever (38 °C or higher).
  - fast heart beat, difficulty breathing,
  - low blood pressure which can make you feel dizzy or lightheaded.

- Effects on your nervous system, symptoms of which can occur days or weeks after you receive the infusion, and may initially be subtle. Some of these symptoms may be signs of a serious immune reaction called 'immune effector cell associated neurotoxicity syndrome' (ICANS) or may be signs and symptoms of parkinsonism:

  Very common (may affect more than 1 in 10 people):
  - feeling confused,
  - less alert, disorientated, anxious, memory loss,
  - difficulty speaking or slurred speech,
  - slower movements, changes in handwriting

  Common (may affect up to 1 in 10 people):
  - loss of coordination, affecting movement and balance,
  - difficulty reading, writing and understanding words,
  - personality changes, which may include being less talkative, disinterest in activities and reduced facial expression

- CARVYKTI may increase the risk of life-threatening infections that may lead to death.

If you notice any of the above side effects, get medical help straight away.

Other side effects
Other side effects are listed below. Tell your doctor or nurse if you get any of these side effects.

Very common (may affect more than 1 in 10 people):
- infected nose, sinuses or throat (a cold)
- bacterial infection
- cough, being short of breath
- headache

- pain, including muscle and joint pain
- stomach pain
- swelling caused by fluid build up in the body
- feeling very tired
- nausea (feeling sick), decreased appetite, constipation, vomiting, diarrhoea

- problems with movement including muscle spasms, muscle tightness
- nerve damage that may cause tingling, numbness, pain or loss of pain sensation
- low levels of antibodies called immunoglobulins in the blood – which may lead to infections
- low level of oxygen in the blood causing shortness of breath, coughing, headache, and confusion
- increased blood pressure

- abnormal blood tests indicating:
  - low number of white blood cells (including neutrophils and lymphocytes) which can occur with infection and fever
  - low levels of 'platelets' (cells that help blood to clot) and red blood cells
  - low levels of calcium, sodium, potassium, magnesium, phosphate in the blood
  - low levels of 'albumin' a type of protein in the blood
  - low levels of 'fibrinogen', a type of protein in the blood, making it more difficult to form clots
  - increased levels of a protein called 'ferritin' in the blood
  - increased levels of enzymes in the blood called 'alkaline phosphatase', 'lactate dehydrogenase', 'gamma-glutamyltransferase' and 'transaminases'

Common (may affect up to 1 in 10 people):
- pneumonia (lung infection)
- viral infection
- fungal infection
- severe infection throughout the body (sepsis)
- a type of herpes virus infection called 'cytomegalovirus'

- kidney failure
- abnormal heart beat
- bleeding, which can be severe, called a 'haemorrhage'
- serious immune reaction involving the blood cells - may lead to an enlarged liver and spleen, called 'haemophagocytic lymphohistiocytosis'

- muscle tremor
- difficulty sleeping
- mild muscle weakness caused by nerve damage
- severe confusion

- tingling, numbness, and pain of hands and feet, difficulty walking, leg and/or arm weakness, and difficulty breathing
- facial numbness, difficulty moving muscles of face and eyes

- high level of 'bilirubin' in the blood
- blood clot
- skin rash
- increased level of a protein called 'C-reactive protein' in the blood that may indicate an infection or inflammation

Tell your doctor or nurse if you get any of the side effects listed above. Do not try to treat your symptoms with other medicines on your own.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store CARVYKTI

The following information is intended for doctors only.

Do not use this medicine after the expiry date which is stated on the container label and infusion bag after 'EXP'.
Store frozen in vapour phase of liquid nitrogen (≤ -120 °C) until thawed for use.
Do not refreeze.

6. Contents of the pack and other information

What CARVYKTI contains
The active substance is ciltacabtagene autoleucel.

Each CARVYKTI infusion bag contains ciltacabtagene autoleucel cell dispersion containing 3.2×10^6 to 1×10^8 CAR-positive viable T cells suspended in a cryopreservative solution.
An infusion bag contains 30 mL or 70 mL of dispersion for infusion.

The other ingredients are a solution (Cryostor CS5) used to preserve frozen cells (see section 2, CARVYKTI contains DMSO and kanamycin).

This medicine contains genetically modified human cells.

What CARVYKTI looks like and contents of the pack
CARVYKTI is a colourless to white, including shades of white, yellow, and pink, 30 ml or 70 ml cell dispersion for infusion, supplied in either a 50 mL or a 250 mL infusion bag respectively, individually packed in an aluminium cryo cassette.

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Manufacturer
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This leaflet was last revised in MM/YYYY.

This medicine has been given 'conditional approval'.
This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu

The following information is intended for healthcare professionals only:

CARVYKTI should not be irradiated as irradiation could inactivate the medicinal product.

Precautions to be taken before handling or administering the medicinal product
CARVYKTI should be transported within the facility in closed, break-proof and leak-proof containers.

This medicinal product contains human blood cells. Healthcare professionals handling CARVYKTI should take appropriate precautions (wearing gloves, protective clothing and eye protection) to avoid potential transmission of infectious diseases.
CARVYKTI must remain ≤ -120°C at all times, until the content of the bag is thawed for infusion.

Preparation prior to administration
The timing of CARVYKTI thaw and infusion should be coordinated; the infusion time should be confirmed in advance, and the start time for thaw must be adjusted so that CARVYKTI is available for infusion when the patient is ready. Once thawed, the medicinal product should be administered immediately and the infusion should be completed within 2.5 hours.

- Prior to CARVYKTI preparation, patient identity should be confirmed by matching the patient's identity with the patient identifiers on the CARVYKTI cryo cassette and Lot Information Sheet.

The CARVYKTI infusion bag should not be removed from the cryo cassette if the information on the patient-specific label does not match the intended patient.

- Once patient identification is confirmed, the CARVYKTI infusion bag should be removed from the cryo cassette.
- The infusion bag should be inspected for any breaches of container integrity such as breaks or cracks before and after thawing. Do not administer if the bag is compromised and contact **Janssen-Cilag International NV**.

Thawing

- The infusion bag should be placed inside a sealable plastic bag prior to thawing.
- CARVYKTI should be thawed at 37°C±2°C using either a water bath or dry thaw device 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.
- The infusion bag should be removed from the sealable plastic bag and wiped dry. The contents of the infusion bag should be gently mixed to disperse clumps of cellular material. If visible cell clumps remain, the contents of the bag should continue to be gently mixed. Small clumps of cellular material should disperse with gentle manual mixing. CARVYKTI must not be pre-filtered into a different container, washed, spun down, and/or resuspended in new media prior to infusion.
- Once thawed, the medicinal product should not be re-frozen or refrigerated.

Administration

- CARVYKTI is for autologous single use only.
- Prior to infusion and during the recovery period, ensure tocilizumab and emergency equipment are available for use. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensure that suitable alternative measures to treat CRS instead of tocilizumab are available on-site.
- Confirm the patient's identity with the patient identifiers on the CARVYKTI infusion bag and Lot Information Sheet. Do not infuse CARVYKTI if the information on the patient-specific label does not match the intended patient.
- Once thawed, the entire contents of the CARVYKTI bag should be administered by intravenous infusion within 2.5 hours at room temperature (20°C to 25°C), using infusion sets fitted with an in-line filter. The infusion usually takes less than 60 min.
- 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 for injection to ensure all medicinal product is delivered.

<u>Precautions to be taken for the disposal of the medicinal product</u>

Unused medicinal product and 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 guidelines on handling of human-derived material.

<u>Measures to take in case of accidental exposure</u>

In case of accidental exposure local guidelines on handling of human-derived material should be followed. Work surfaces and materials which have potentially been in contact with CARVYKTI must be decontaminated with appropriate disinfectant.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for ciltacabtagene autoleucel, the scientific conclusions of the PRAC are as follows:

In view of available data on leak from bags of CARVYKTI after thawing from clinical trial(s) and spontaneous reports including in a close temporal relationship, the PRAC considers that a causal relationship between ciltacabtagene autoleucel and product handling issues is at least a reasonable possibility. As well, even though further investigation is warranted in regards to the case of T-Cell Malignancy, the mention of such case has been considered acceptable as intermediary action in the section 4.4 of the SmPC. The PRAC concluded that the product information of products containing ciltacabtagene autoleucel should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for ciltacabtagene autoleucel the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing ciltacabtagene autoleucel is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.