CAR-T Cell Therapy with Ciltacabtagene Autoleucel▼: Information for CAR-T Centre Healthcare Providers

Ciltacabtagene autoleucel
CARVYKTI®

Version 1 , June 2022

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Sections with a light blue background are part of the mandatory Risk Management Plan (RMP) for ciltacabtagene autoleucel

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CAR-T cell therapy

- Ciltacabtagene autoleucel (cilta-cel) is a B-cell maturation antigen (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 ciltacabtagene autoleucel 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.[1]
- Ciltacabtagene autoleucel is indicated for the treatment of adults with relapsed or refractory multiple myeloma who received at least three prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor and an immunomodulatory agent.[1]
- After reprogramming, T cells acquire pharmacological activity that gives them the status of drugs.
- CAR-T centres bring together multidisciplinary specialists and resources, providing the infrastructure to ensure a smooth process for CAR-T cell therapy patients.
- Despite its potential, CAR-T cell therapy is associated with adverse events following infusion that can be life-threatening. These include cytokine release syndrome (CRS) and neurologic toxicities.[1]
- This guide aims to educate CAR-T centre healthcare providers on the appropriate management of important selected risks associated with ciltacabtagene autoleucel.

1. CARVYKTI 0.15 to 1 x 10^8 cells dispersion for infusion. Summary of Product Characteristics, 2021.

Your role within the CAR-T multidisciplinary team

- This guide is aimed at all HCPs (e.g., physicians, nurses, pharmacists and ward staff) who prescribe, dispense or administer ciltacabtagene autoleucel and will give a short introduction on:
  - Guidance for the identification, monitoring and treatment of adverse events associated with CAR-T cell therapy. Please refer to the CARVYKTI Summary of Product Characteristics (SPC), local guidelines or centre-specific protocols for further detail.
  - Efficient interactions between the haematologist, nurse, neurologist, ICU specialist, pharmacist, other multidisciplinary team members and the patient/caregiver.
  - The need for each aspect of the CAR-T cell therapy process to be explained to the patient, including associated risks.
  - Encouragement of patient reporting of any adverse reactions that may occur.

The CAR-T cell therapy process

There are five steps involved in CAR-T cell therapy:

START

Patient eligibility assessment

STEP 1

Apheresis

STEP 2

Bridging therapy (not mandatory)

STEP 3

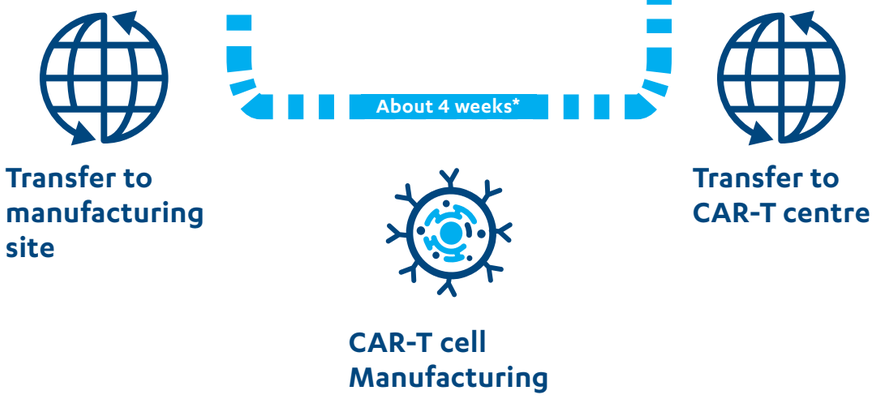
Lymphodepleting chemotherapy

STEP 4

CAR-T cell infusion

STEP 5

Short- and long-term monitoring



Referring centre

CAR-T centre

Timepoint for patient eligibility check to allow continuation to next step

*In the MMY2001 study, the median time from the day after receipt of leukapheresis material at the manufacturing facility to release of product for infusion was 29 days (range 23–64 days) and the median time from initial leukapheresis to ciltacabtagene autoleucel infusion was 47 days (range 41–167 days).

The CAR-T cell therapy process

Patient eligibility for CAR-T cell therapy

- It is important that patients are made aware of the many steps and difficulties that can arise throughout the process. Patients need to be carefully selected in order to manage their expectations.
- Clinical judgement in line with Summary of Product Characteristics (SPC) criteria should be employed to assess eligibility, and should include all relevant medical staff.
- Patient eligibility for CAR-T cell therapy can vary throughout the process, so selection checklists should be appropriately adaptable.
- Re-assessment of eligibility for CAR-T cell infusion occurs after the patient has undergone bridging therapy, and again after lymphodepleting chemotherapy. This is carried out by the CAR-T centre physician. These are known as 'green light' checks on the patient's clinical status to confirm they can proceed.
- The eligibility assessment should also include the assessment of pre-existing malignancy (i.e. patients with a history of first or higher order primary cancer diagnosed prior to myeloma).
- There is currently no experience with manufacturing ciltacabtagene autoleucel for patients testing positive for HIV, active HBV, or active HCV. Screening for HBV, HCV and HIV must be performed before collection of cells for manufacturing.[1]

Apheresis (or leukapheresis)

- Apheresis involves removing autologous blood mononuclear cells from the patient, after which they will be packaged and sent to the CAR-T cell manufacturing facility. Apheresis can take 3–6 hours and may need to be repeated.
- Please note, patients are required to undergo a wash-out period for certain medications before undergoing apheresis. For example, EBMT-JACIE recommendations advise discontinuation of corticosteroids for 7 days prior to apheresis. Please refer to Yakoub-Agha et al. (2020, Haematologica, 105[2]:297–316) or local guidelines for further information.

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Bridging therapy

- Bridging therapy may be given to the patient during cell processing and manufacturing, and is designed to reduce the risk of disease progression during this “waiting” period. This may include chemotherapy, immunomodulatory drugs, radiation therapy or corticosteroids.
- Bridging therapy can take place at the patient’s referring centre, requiring close communication between the CAR-T site and the patient’s local medical team. This includes a report on the outcome of bridging therapy, as well as the performance status of the patient and any toxicities experienced.
- Following apheresis and prior to administration of ciltacabtagene autoleucel in the CARTITUDE-1 trial (NCT03548207), 73 (75%) of the 97 patients received bridging therapy. The most commonly used agents as bridging therapies (≥20% of patients) included dexamethasone: 62 subjects (63.9%), bortezomib: 26 subjects (26.8%), cyclophosphamide: 22 subjects (22.7%), and pomalidomide: 21 subjects (21.6%).[1]

Lymphodepleting chemotherapy

- The availability of ciltacabtagene autoleucel should be confirmed prior to starting the lymphodepleting regimen.[1]
- The 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).[1]
- The lymphodepleting chemotherapy regimen is well defined and usually provided by the CAR-T centre – administration of intravenous cyclophosphamide (300 mg/m^2) and intravenous fludarabine (30 mg/m^2) daily for 3 days takes place to achieve lymphodepletion 5–7 days before the CAR-T cell infusion.[1]
- In exceptional cases, lymphodepleting chemotherapy may be administered at the patient’s referring centre if it is JACIE-accredited. This requires close communication between the CAR-T site and the patient’s local medical team, including a report on the outcome of lymphodepleting chemotherapy, the performance status of the patient and any toxicities experienced.
- The approach to lymphodepletion is influenced by patient characteristics – e.g., renal impairment, presence of infection or lymphocyte count. These parameters should be monitored and local guidelines referred to.

- Common adverse events may include low blood count and infection. If resolution of toxicities due to the lymphodepleting regimen to Grade 1 or lower takes more than 14 days, thereby resulting in delays to ciltacabtagene autoleucel dosing, the lymphodepleting regimen should be re-administered after a minimum of 21 days following the first dose of the first conditioning regimen.[1]

Clinical assessment prior to infusion and prevention of adverse events

- Avoid use of prophylactic systemic corticosteroids as it may interfere with the activity of ciltacabtagene autoleucel.[1]
- Baseline neurological assessments should be carried out (in accordance with local standard operating procedures) in order to detect any changes in behavioural or cognitive function, or any other new appearing neurological sign, after CAR-T cell infusion. These should be determined by the neurologist and tailored to the patient.
- These can include:
  - Screening tests for cognitive dysfunction (e.g., Montreal Cognitive Assessment [MOCA], Mini-Mental State Examination [MMSE], Immune Effector Cell-associated Encephalopathy [ICE])
  - Magnetic resonance imaging (MRI) scan
  - Computed tomography (CT) scan
  - Electroencephalogram (EEG)
- Patient/caregiver-reported outcome measures on quality of life can be useful in addition to neurological assessments.

- 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 adverse reactions and require special attention.[1]
- Appropriate prophylactic and therapeutic treatment for infections should be provided. Complete resolution of any active infections should be ensured prior to ciltacabtagene autoleucel infusion. Infections may also occur concurrently with CRS and may increase the risk of a fatal event.[1]
- Infusion should be delayed if a patient has any of the following conditions:
  - Clinically significant active infection.[1]

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  - Grade ≥3 non-haematologic toxicities of cyclophosphamide and fludarabine conditioning except for Grade 3 nausea, vomiting, diarrhoea, or constipation. Ciltacabtagene autoleucel infusion should be delayed until resolution of these events to Grade ≤1.[1]
- Consider reducing baseline burden of disease with bridging therapy prior to infusion with ciltacabtagene autoleucel in patients with high tumor burden which may mitigate the risk of developing neurologic toxicity.[1]

CAR-T cell infusion

- The following pre-infusion medications should be administered to all patients (30 mins to 1 h) prior to ciltacabtagene autoleucel infusion:
  - Antipyretics (oral or intravenous paracetamol 650 to 1000 mg).[1]
  - Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).[1]
- The product must not be thawed until it is ready to be used. The timing of the ciltacabtagene autoleucel 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 ciltacabtagene autoleucel is available for infusion when the patient is ready. The product should be administered immediately after thawing and the infusion should be completed within 2.5 hours of thawing.[1]
- Ciltacabtagene autoleucel is for intravenous use only (please refer to the SmPC or the ciltacabtagene autoleucel Handling Guide for full details on the handling and preparation of ciltacabtagene autoleucel infusion and the administration process).

Adverse events: CRS and neurologic toxicities

- Potential adverse events associated with CAR-T cell therapy include (among others) CRS and neurologic toxicities.
- These adverse events will be managed by CAR-T centre HCPs.
- Monitor patients daily for 14 days after the ciltacabtagene autoleucel infusion at a qualified clinical facility and then periodically for an additional two weeks after ciltacabtagene autoleucel infusion for signs and symptoms of CRS, neurologic events and other toxicities.[1]
- Patients should be instructed to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion.[1]
- Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time or if signs and symtoms of neurologic toxicities occur after recovery from CRS and/or ICANS.[1]

Adverse events: CRS

Symptoms[1,*]	• Fever (with or without rigors), chills, hypotension, hypoxia, elevated liver enzymes. Potentially life-threatening complications of CRS may include cardiac dysfunction, neurologic toxicity, and haemophagocytic lymphohistiocytosis (HLH). Evaluation for HLH should be considered in patients with severe or unresponsive CRS. • Neurologic signs and symptoms may occur concurrently with CRS, following resolution of CRS or in the absence of CRS.
Risk factors[1]	• High pre-infusion tumour burden, active infection and early onset of fever or persistent fever after 24 hours of symptomatic treatment.
Incidence[1,*]	• In study MMY2001, CRS was reported in the majority (95%) of patients; 90% CRS events were Grade 1 or Grade 2, 4% were Grade 3 or Grade 4 and 1% was Grade 5. Ninety-nine percent of patients recovered from CRS.
Time to onset*	• Time to onset of CRS may vary between CAR-T cell therapies. In clinical studies, the median time from ciltacabtagene autoleucel infusion and first onset of CRS was **7 days (range: 1–12 days)**.[1] This is typically later than other commercially-available CAR-T cell therapies. Approximately 90% of patients experienced onset of CRS after day 3 of receiving the ciltacabtagene autoleucel infusion.[1]
Duration[1,*]	• Median duration of CRS was 4 days, which ranged from 1 to 14 days for all but one patient who had a duration of CRS of 97 days complicated by secondary HLH with a subsequent fatal outcome. Eighty eight percent of patients had CRS with a duration of ≤7 days.

*Data from clinical studies
1. CARVYKTI 0.15 to 1 x 10^8 cells dispersion for infusion. Summary of Product Characteristics, 2021.

Adverse events: CRS

Monitoring[1]	• Patients should be monitored daily for 14 days at a qualified clinical facility and then periodically for an additional two weeks following infusion for signs and symptoms of CRS. Frequency of monitoring should be increased if CRS occurs. • Monitoring parameters include: temperature, blood pressure, heart rate and oxygen saturation. Patients should be counselled to seek immediate medical attention should signs or symptoms of CRS occur at any time.
Grading	• Please refer to your centre's CAR-T cell standard operating procedure (SOP) or guidelines in order to grade CRS. • The most current grading system for CRS has been developed by the American Society for Transplantation and Cellular Therapies (ASTCT); this is provided in the appendix.
Management[1]	• Ensure at least one dose of tocilizumab is available on-site prior to ciltacabtagene autoleucel infusion, with access to an additional dose within 8 hours of each previous dose. • At the first sign of CRS, immediately evaluate the patient for hospitalisation and institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids as indicated in Table 1 below.

Table 1: CRS management

Grade	Presenting Symptoms	Tocilizumab[a]	Corticosteroids[b]
Grade 1	Temperature ≥38°C[c]	• May be considered	• N/A
Grade 2	Temperature ≥38°C[c] with either: • Hypotension responsive to fluids and not requiring vasopressors. • Or, oxygen requirement of low-flow nasal canula[d] or blow-by.	• Administer tocilizumab[b] 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). • Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. • Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	• Manage per guidance below if no improvement within 24 hours of starting tocilizumab.

	Grade	Presenting Symptoms	Tocilizumab[a]	Corticosteroids[b]
Management (continued)	Grade 3	Temperature ≥38°C[c] with either: • Hypotension requiring one vasopressor with or without vasopressin. • Or, oxygen requirement of high-flow nasal cannula[d], facemask, non-rebreather mask, or Venturi mask.	• Administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). • Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. • Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	• If no improvement, administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (eg, 10 mg intravenously every 6 hours). • Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days.
	Grade 4	Temperature ≥38°C[c] with either: • Hypotension requiring multiple vasopressors (excluding vasopressin). • Or, oxygen requirement of positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation).	• Administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). • Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. • Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	• As above, or administer methylprednisolone 1000 mg intravenously per day for 3 days per investigator discretion. • If no improvement or if condition worsens, consider alternate immunosuppressants.[b]

- 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 remains severe or life-threatening following prior administration of tocilizumab and corticosteroids.
- 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 GM-CSF, should be avoided during CRS.
- Supportive care for CRS (including, but not limited to, anti-pyretic agents, IV fluid support, vasopressors, supplemental oxygen, etc.) should be administered as appropriate. Consider laboratory testing to monitor for disseminated intravascular coagulation, haematology parameters, as well as pulmonary, cardiac, renal and hepatic function.

a) Refer to tocilizumab prescribing information for details; b) Monoclonal antibodies targeting cytokines may be considered based on institutional practice for unresponsive CRS; 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 anticytokine therapy (eg, tocilizumab or steroids); d) Low-flow nasal cannula is ≤6 L/min, and high-flow nasal cannula is >6 L/min.
1. CARVYKTI 0.15 to 15 x 10^8 cells dispersion for infusion. Summary of Product Characteristics, 2021.

Adverse events: Neurologic toxicities

Symptoms[1,*]	• Symptoms of ICANS included: aphasia, slow speech, dysgraphia, encephalopathy, depressed level of consciousness and confusional state. • Symptoms of adverse reactions of neurologic toxicity after recovery from CRS and/or ICANS included: disturbances in consciousness, coordination and balance disturbances, movement disorders, mental impairment disorders, cranial nerve disorders, and peripheral neuropathies.
Incidence[1,*]	• Neurologic toxicities occur frequently following treatment with ciltacabtagene autoleucel and can be fatal or life-threatening. • In study MMY2001, neurologic toxicity occurred in 21% of patients, with 8% being Grade 3/4 and 1% Grade 5. • Events of ICANS were reported for 16% of patients, of which 2% had Grade 3 or higher ICANS. • Adverse reactions of neurologic toxicity after recovery from CRS and/or ICANS was observed in 12% of patients.[†]
Time to onset[1,*]	• The onset of neurological toxicity can be concurrent with CRS, following resolution of CRS or in the absence of CRS. • The median time from ciltacabtagene autoleucel infusion to first onset of ICANS was **8 days (range: 3 to 12 days)**. • Median time from ciltacabtagene autoleucel infusion to symptoms of adverse reactions of neurologic toxicity after recovery from CRS and/or ICANS was **26.5 days (range: 11 to 108 days)**.
Duration[1,*]	• Median duration of ICANS was **4 days (range: 1 to 12 days)**. • Median time to recovery of adverse reactions of neurologic toxicity after recovery from CRS and/or ICANS was **74.5 days (range: 2 to 160 days)**.
Monitoring	• Monitor patients for signs or symptoms of ICANS for four weeks after infusion. They should also be monitored for signs or symptoms of neurotoxicity occurring after recovery from CRS and/or ICANS.[1] • Baseline neurological characteristics (e.g., behavioural, cognitive, EEG, CT/MRI scans) of patients should be known prior to CAR-T cell infusion to assist with detection of neurologic toxicities following treatment. • At the first sign of neurologic toxicity including ICANS, neurology evaluation should be considered. Rule out other causes of neurologic symptoms.[1] • Counsel patients to seek immediate medical attention should signs and symptoms of neurologic toxicities occur after recovery from CRS and/or ICANS.[1]

*Data from clinical studies. †In study MMY2001, five percent of patients (all male) experienced a cluster of movement and neurocognitive adverse reactions including movement (e.g., micrographia, tremors), cognitive (e.g., memory loss, disturbance in attention), and personality change (e.g., reduced facial expression, flat affect), often with subtle onset (e.g., micrographia, flat affect), that in some patients progressed to an inability to work or care for oneself. The median time to first symptom onset was 27 days (range 14 to 108 days). These patients all presented a combination of two or more factors such as high tumor burden (bone marrow plasma cell ≥80% or serum M-spike ≥5 g/dL or serum free light chain ≥5000 mg/L), prior Grade 2 or higher CRS, prior ICANS, and high CAR-T cell expansion and persistence. Treatment with levodopa/carbidopa was not effective in improving symptomatology in these patients.
1. CARVYKTI 0.15 to 1 x 10^8 cells dispersion for infusion. Summary of Product Characteristics, 2021.

Grading

- Please refer to your centre's CAR-T cell standard operating procedure (SOP) or guidelines in order to grade neurotoxicity.
- The most current grading system for ICANS has been developed by the American Society for Transplantation and Cellular Therapies (ASTCT). ASTCT ICANS consensus grading for adults incorporates the ICE score. Please see appendix for ASTCT ICANS Consensus Grading system for Adults and ICE score.

Management

- 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.

Table 2: ICANS management[1]

ICANS Grade[a]	Presenting Symptoms[b]	Concurrent CRS	No Concurrent CRS
Grade 1	ICE score 7–9[c] or depressed level of consciousness[d]: awakens spontaneously.	Management of CRS per Table 1.	Consider dexamethasone.
Grade 2	ICE score-3–6[c] or depressed level of consciousness[d]: awakens to voice.	Administer tocilizumab per Table 1 for management of CRS. If no improvement after starting tocilizumab, administer 10 mg IV dexamethasone[e] every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until resolution to ≤Grade 1 then taper.	Administer 10mg IV dexamethasone[e] every 6 hours. Continue dexamethasone use until resolution to ≤Grade 1, then taper.
Grade 3	ICE score-0–2[c] or depressed level of consciousness[d]: awakens only to tactile stimulus, or seizures[d], either: • any clinical seizure, focal or generalised, that resolves rapidly, or • non-convulsive seizures on EEG that resolve with intervention, or raised ICP: focal/local oedema on neuroimaging[d].	Administer tocilizumab per Table 1 for management of CRS. In addition, administer dexamethasone[e] 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until resolution to ≤Grade 1, then taper.	Administer dexamethasone[e] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to ≤Grade 1, then taper.

Management (continued)

ICANS Grade[a]	Presenting Symptoms[b]	Concurrent CRS	No Concurrent CRS
Grade 4	ICE score-0[c] or depressed level of consciousness[d] either: • patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, or seizures[d], either: • life-threatening prolonged seizure (>5 min), or • repetitive clinical or electrical seizures without return to baseline in between, or motor findings[d]: • deep focal motor weakness such as hemiparesis or paraparesis, or raised ICP / cerebral oedema[d], 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 tocilizumab per Table 1 for management of CRS. As above or consider administration of IV methylprednisolone 1000 mg per day with first dose of tocilizumab and continue IV methylprednisolone 1000 mg per day for 2 or more days. In case of raised ICP/cerebral oedema, refer to institutional guidelines for management.	As above or consider administration of IV methylprednisolone 1000 mg per day for 3 days; if improves, then manage as above.

- Consider reducing baseline burden of disease with bridging therapy prior to infusion with ciltacabtagene autoleucel in patients with high tumor burden, which may mitigate the risk of developing neurologic toxicity. Early detection and aggressive treatment of CRS or ICANS may be important to prevent neurologic toxicity from occurring or worsening.[1]
- Provide intensive care and supportive therapy for severe or life-threatening neurologic toxicities.[1]
- Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis for any grade ICANS.[1]
- It is advisable that outpatients presenting with neurotoxicities are transferred to their CAR-T treatment centre. It is important that communication channels are open between the patient's local hospital and the CAR-T treatment centre as delayed admission (when the patient's neurotoxicities are Grade 3 or higher) could be associated with worse prognostic outcomes.

a) Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis for any grade ICANS; b) Management is determined by the most severe event, not attributable to any other cause; c) If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess: **Orientation** (oriented to year, month, city, hospital = 4 points); **Naming** (name 3 objects, e.g., point to clock, pen, button = 3 points); **Following Commands** (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue" = 1 point); **Writing** ability to write a standard sentence = 1 point; and Attention (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points; d) Attributable to no other cause; e) All references to dexamethasone administration are dexamethasone or equivalent.

Provision of patient information

It is very important to instruct patients and caregivers that they need to remain **within proximity** of the qualified clinical facility for at least 4 weeks following infusion and to **seek immediate medical attention** should signs or symptoms of **CRS or neurologic toxicities occur at any time.**

Symptoms to look out for:

- Chills, fever (38°C or higher, which can also be a sign of infection), fast heart beat, difficulty breathing, low blood pressure which can make the patient feel dizzy or lightheaded. These may be signs of a serious immune reaction known as 'cytokine release syndrome' (CRS).
- Effects on the nervous system, which can occur days or weeks after infusion, and may initially be subtle:
  - Feeling confused, less alert, disorientated, anxious or having memory loss
  - Difficulty speaking or slurred speech
  - Slower movements, changes in handwriting
  - Loss of coordination, affecting movement and balance
  - Having difficulty reading, writing and understanding words
  - Personality changes which may include being less talkative, disinterest in activities and reduced facial expression

  Some of these symptoms may be signs of a serious immune reaction called `immune effector cell-associated neurotoxicity syndrome' (ICANS).

If the patient or their caregiver notice **any symptoms** of CRS or neurologic toxicities at **any time** then they must **contact the CAR-T centre immediately.**

- Patients will be provided with '**My CAR-T Journey Guide**', which will explain what to expect at all stages of the CAR-T process.
- Patients/caregivers should carry the **patient card for ciltacabtagene autoleucel** at all times to remind them of the signs and symptoms of CRS and neurological toxicities that require immediate attention. Counsel the patient to share it with any healthcare professional involved in their treatment.

Other adverse events

Adverse events: Prolonged cytopenia[1]

Symptoms

- Fever, fatigue, weakness, frequent infections, bleeding and easy bruising.

Incidence*

- In study MMY2001 the nearly all patients had one or more Grade 3 or 4 cytopenic adverse reactions.

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

a) The lab result with the worst toxicity grade will be used for a calendar day. Recovery definition: must have 2 consecutive Grade ≤2 results on different days if recovery period ≤10 days.
Notes: Lab results assessed after Day 1 until Day 100 are included in the analysis. Thrombocytopenia: Grade 3/4 – Platelets count <50,000 cells/µL. Neutropenia: Grade 3/4 - Neutrophil count <1000 cells/µL. Lymphopenia: Grade 3/4 - Lymphocytes count <0.5×10^9 cells/L. Percentages are based on the number of treated patients.

Time to onset*

- 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.

Management

- Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and ciltacabtagene autoleucel infusion, and should be managed according to local guidelines.
- Blood counts should be monitored after ciltacabtagene autoleucel infusion. For thrombocytopenia, supportive care with transfusions should be considered. Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, particularly granulocyte macrophage-colony stimulating factor (GM-CSF), have the potential to worsen CRS symptoms and are not recommended during the first 3 weeks after ciltacabtagene autoleucel or until CRS has resolved.

*Data from clinical studies.

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Adverse events: Serious infections and febrile neutropenia[1]

Incidence*	• Infections occurred in 58% of patients in Study MMY2001, 20% of patients experienced Grade 3 or Grade 4 infections, and fatal infections occurred in 3% of patients (lung abscess, sepsis, and septic shock). The most frequently reported Grade ≥3 (≥5%) infections were pneumonia and sepsis. • Febrile neutropenia was observed in 10% patients with 4% experiencing serious febrile neutropenia.
Monitoring	• Patients should be monitored for signs and symptoms of infection prior to and during treatment with ciltacabtagene autoleucel and treated appropriately. Infections are known to complicate the course and management of concurrent CRS.
Management	• Prophylactic antimicrobials should be administered according to local guidelines. • Patients with clinically significant active infection should not start ciltacabtagene autoleucel 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.

Adverse events: Hypogammaglobulinemia[1]

Incidence*	• Hypogammaglobulinemia may occur in subjects receiving ciltacabtagene autoleucel. Hypogammaglobulinemia occurred in 11% of patients, with 2% of patients experiencing Grade 3 or 4 hypogammaglobulinemia.
Monitoring	• Monitor immunoglobulin levels after treatment.
Management	• Treat according to standard guidelines, including administration of immunoglobulin replacement, antibiotic prophylaxis and monitoring for infection.

Viral reactivation[1]

General	• HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death can occur in patients treated with drugs directed against B cells. • There is currently no experience with manufacturing ciltacabtagene autoleucel for patients testing positive for HIV active HBV, or active HCV. Screening for HBV, HCV and HIV must be performed in accordance with clinical guidelines before collection of cells for manufacturing.

*Data from clinical studies

1. CARVYKTI 0.15 to 1 x 10^6 cells dispersion for infusion. Summary of Product Characteristics, 2021.

Secondary malignancies[1]

General	• Patients treated with ciltacabtagene autoleucel may develop secondary malignancies. Patients should be monitored life-long for secondary malignancies. In the event that a secondary malignancy occurs, Jansen-Cilag should be contacted to obtain instructions on patient samples to collect for testing.

Hypersensitivity[1]

General	• Allergic reactions may occur with infusion of ciltacabtagene autoleucel. Serious hypersensitivity reactions, including anaphylaxis, may occur due to the dimethyl sulfoxide (DMSO) or residual kanamycin in ciltacabtagene autoleucel.

Long-term monitoring

Length of follow-up period

- After discharge from the CAR-T centre, the CAR-T team will receive regular updates from the referring centre regarding the patient's intermediate- and long- term outcomes.
- Patients will be asked to enrol in a registry for at least 15 years in order to better understand the long-term effects of ciltacabtagene autoleucel.[1]

Additional considerations

COVID-19

- Please follow all national guidance and adhere to all national restrictions.

Effects on ability to drive and use machines[1]

- Due to the potential for neurologic events, patients receiving ciltacabtagene autoleucel are at risk for altered or decreased consciousness or coordination in the 4 weeks following ciltacabtagene autoleucel infusion.
- 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.

Blood, organ, tissue, and cell donation[1]

- Patients treated with ciltacabtagene autoleucel should not donate blood, organs, tissues, or cells for transplantation.

Live vaccines[1]

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

Interference with serological testing[1]

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

Women of childbearing potential/contraception in males and females[1]

- Pregnancy status for females of child-bearing age should be verified prior to starting treatment with ciltacabtagene autoleucel.
- There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with ciltacabtagene autoleucel.
- See the prescribing information for lymphodepleting chemotherapy for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

Pregnancy[1]

- There are no available data on the use of ciltacabtagene autoleucel in pregnant women, and no reproductive and developmental toxicity animal studies have been conducted with ciltacabtagene autoleucel. It is not known whether ciltacabtagene autoleucel has the potential to be transferred to the foetus and cause foetal toxicity. Therefore, ciltacabtagene autoleucel 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 ciltacabtagene autoleucel therapy should be discussed with the treating physician.
- Pregnant women who have received ciltacabtagene autoleucel may have hypogammaglobulinaemia. Assessment of immunoglobulin levels in newborns of mothers treated with ciltacabtagene autoleucel should be considered.

Breast-feeding[1]

- It is unknown whether ciltacabtagene autoleucel 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 ciltacabtagene autoleucel, the decision to consider breast-feeding should be discussed with the treating physician.

Fertility[1]

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

1. CARVYKTI 0.15 to 1 x 10^8 cells dispersion for infusion. Summary of Product Characteristics, 2021.

Glossary

ASTCT	American Society for Transplantation and Cellular Therapies
BCMA	B-cell maturation antigen
CAR	Chimeric antigen receptor
CRS	Cytokine release syndrome
CT	Computed tomography
EBMT-JACIE	European Society for Blood and Bone Marrow Transplantation-Joint Accreditation Committee ISCT-Europe & EBMT
EEG	Electroencephalogram
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HBV	Hepatitis B
HCP	Healthcare professional
HCV	Hepatitis C
HIV	Human immunodeficiency virus
HLH	Haemophagocytic lymphohistiocytosis
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICE	Immune effector cell-associated encephalopathy
ICP	Intracranial pressure
ICU	Intensive care unit
MMSE	Mini mental state examination
MOCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
NATs	Nucleic acid tests
RNA	Ribonucleic acid
RMP	Risk management plan
SPC	Summary of product characteristics

Reporting of adverse events

- 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 SFDA (National Pharmacovigilance Center):
  Email: npc.drug@sfda.gov.sa
  Telephone: 19999
  Fax: +966 11 2057662
  Online: http://ade.sfda.gov.sa

  For full prescribing information, please refer to the datasheet or contact Johnson & Johnson Middle East FZ-LLC (Riyadh)
  Address: Prince Muhammed Bin Abdulaziz Rd, Tower B, Level 30, Olaya towers.
  Office Tel: 00966-11-4339133
  Postal address: P O Box 65305 Riyadh 11556, Saudi Arabia
  To Report Adverse Events/Product Complaint or Any Medical Information Inquiries, please contact us at:
  Email: GCC-PV2@its.jnj.com
  Hotline: 00966540015811

- In order to improve the traceability of ciltacabtagene autoleucel, the tradename and the batch number of the administered product should be clearly recorded when reporting an adverse event.
- When reporting a suspected adverse reaction, please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment date.

Appendix

ASTCT CRS Consensus Grading*[Lee 2019]

	Grade 1	Grade 2	Grade 3	Grade 4
Fever†	≥38°C	≥38°C	≥38°C	≥38°C
With either:				
Hypotension	None	Not requiring vasopressors	Requiring 1 vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or*				
Hypoxia	None	Requiring low-flow nasal cannula§ or blow-by	Requiring high-flow nasal cannula,§ facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (e.g., continuous positive airway pressure, bilevel positive airway pressure, intubation and mechanical ventilation)

*ASTCT was previously known as ASBMT, the American Society for Blood and Marrow Transplantation. Organ toxicities associated with CRS may be graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, but they do not influence CRS grading. †Fever is defined as a temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretics or anti-cytokine therapy, such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia. *CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with a temperature of 39.5°C, hypotension requiring 1 vasopressor and hypoxia requiring low-flow nasal cannula is classified as having Grade 3 CRS. §Low-flow nasal cannula is defined as oxygen delivered at <6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/min.

Lee DW, et al. Biol Blood Marrow Transplant. 2019;25(4):625–38.

ASTCT ICANS Consensus Grading for Adults*[Lee 2019]

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score†	7–9	3–6	0–2	0 (patient unarousable and unable to perform ICE)
Depressed level of consciousness‡	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure, focal or generalized that resolves rapidly; or non-convulsive seizures on electroencephalogram that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings§	N/A	N/A	N/A	Deep focal motor weakness, such as hemiparesis or paraparesis
Raised intracranial pressure (ICP)/ cerebral oedema	N/A	N/A	Focal/local oedema on neuroimaging‖	Diffuse cerebral oedema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

*ICANS grade 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. For example, a patient with an ICE score of 3 who has a generalized seizure is classified as having Grade 3 ICANS. †A patient with an ICE score of 0 may be classified as having Grade 3 ICANS if the patient is awake with global aphasia. But a patient with an ICE score of 0 may be classified as having Grade 4 ICANS if the patient is unarousable. ‡Depressed level of consciousness should be attributable to no other cause (e.g., no sedating medication). §Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE version 5.0, but they do not influence ICANS grading. ‖Intracranial hemorrhage with or without associated oedema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE version 5.0.

Lee DW, et al. Biol Blood Marrow Transplant. 2019;25(4):625–38.

ICE Score[Lee 2019]

Domain	Description	Total Points
Orientation	Orientation to year, month, city, hospital	4 points
Naming	Ability to name 3 objects; e.g., "Point to clock"	3 points
Following commands	Ability to follow simple commands; e.g., "Show me 2 fingers" or "Close your eyes and stick out your tongue"	1 point
Writing	Ability to write a standard sentence; e.g., "Our national bird is the bald eagle"	1 point
Attention	Ability to count backwards from 100 by 10	1 point

Notes

Notes

Version 1 , June 2022