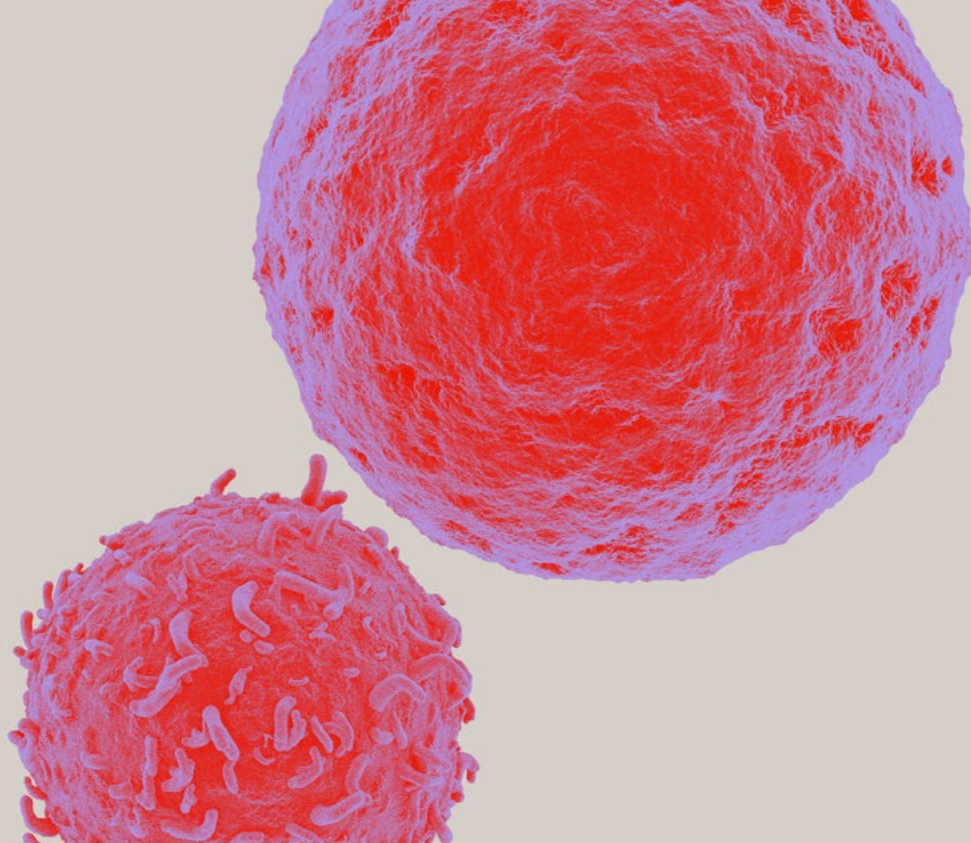




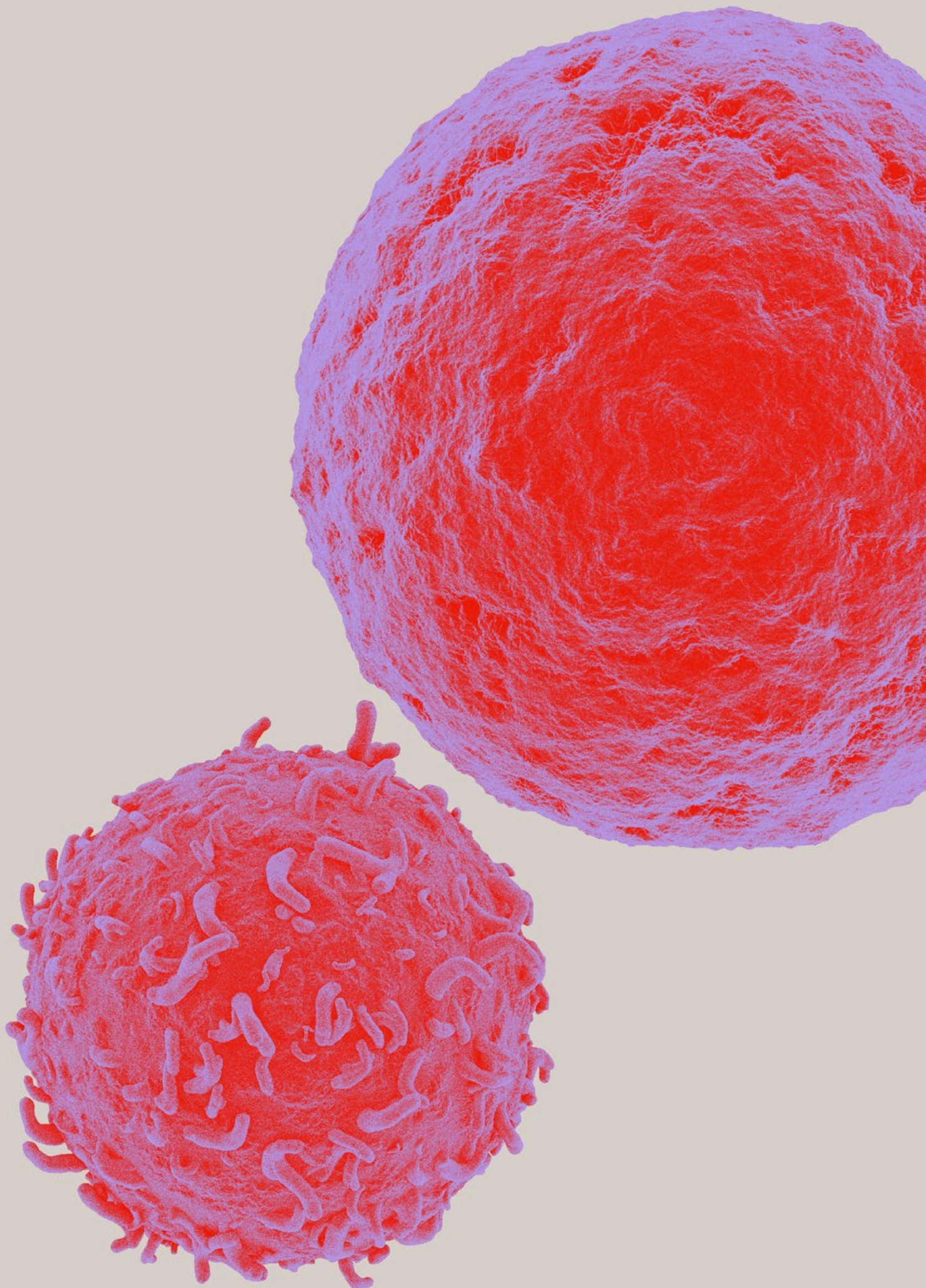
CAR-T Cell Therapy with Ciltacabtagene Autoleucel: Information for CAR-T Centre Healthcare Professionals

Ciltacabtagene autoleucel
CARVYKTI®▼

Adverse events should be reported. ▼ 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 events via: HPRA Pharmacovigilance, Website: www.hpra.ie. Adverse events should also be reported to Janssen Sciences Ireland UC, a Johnson & Johnson Company, on +44 1494 567447 or at dsafety@its.jnj.com.

Johnson & Johnson

This guide has been approved by the HPRA
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CAR-T cell therapy	4
Your role within the CAR-T multidisciplinary team	5
Clinical assessment prior to infusion and prevention of adverse events	6–7
Adverse events: CRS	8–13
Adverse events: Neurologic toxicities	14–21
Provision of patient information	22–23
Other adverse events	23
Available resources	24
Glossary	25–26
Reporting of adverse events	27
Appendix	28–30
Notes	31–34

CAR-T cell therapy

- Ciltacabtagene autoleucel 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) signalling 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 adult patients with relapsed and refractory multiple myeloma who have received at least one prior therapy, including an immunomodulatory agent and a proteasome inhibitor, have demonstrated disease progression on the last therapy, and are refractory to lenalidomide.¹
- 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 professionals (HCPs) on the appropriate management of important selected risks associated with ciltacabtagene autoleucel.

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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 provide guidance on:
 - Increased 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.
 - The need for patient counselling of relevant information, including counselling on the 'My CAR-T Journey Guide' and the Patient Alert Card.
 - Reporting of these serious adverse reactions associated with CARVYKTI®.
 - Ensuring 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.
 - Risks of secondary malignancy of T-cell origin and myeloid origin.

Clinical assessment prior to infusion and prevention of adverse events

- The use of prophylactic systemic corticosteroids should be avoided as it may interfere with the activity of ciltacabtagene autoleucel.¹
- 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. There is no experience of use of ciltacabtagene autoleucel in patients with CNS involvement of myeloma or other pre-existing, clinically relevant CNS illnesses.¹
- Appropriate prophylactic and therapeutic treatment for infections should be provided, and 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
- Ciltacabtagene autoleucel infusion should be delayed if a patient has any of the following conditions:
 - Clinically significant active infection or inflammatory disorders.¹
 - Grade ≥ 3 non-haematologic toxicities of cyclophosphamide and fludarabine lymphodepletion regimen, except for Grade 3 nausea, vomiting, diarrhoea, or constipation. Ciltacabtagene autoleucel infusion should be delayed until resolution of these events to Grade ≤ 1 .¹
 - Active graft versus host disease.¹
- Reduction of baseline burden of disease with bridging therapy prior to infusion with ciltacabtagene autoleucel in patients with high tumour burden should be considered, which may mitigate the risk of developing neurologic toxicity.¹

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CAR-T cell infusion

- The following pre-infusion medications should be administered to all patients 30 to 60 minutes prior to ciltacabtagene autoleucel infusion:
 - Antipyretic (oral or IV paracetamol 650 to 1,000 mg).¹
 - Antihistamine (oral or IV diphenhydramine 25 to 50 mg or equivalent).¹
- The medicinal product must not be thawed until it is ready to be used.
The timing of 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 medicinal product should be administered immediately after thawing and the infusion should be completed within 2.5 hours of thawing.¹
- Ciltacabtagene autoleucel is for IV use only¹ (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).

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Adverse events: CRS

- 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.
- Patients should be monitored daily for 14 days after the ciltacabtagene autoleucel infusion at a qualified clinical facility and then periodically for an additional 2 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
- Patients should be counselled to seek immediate medical attention should signs or symptoms of CRS occur at any time.¹

Adverse events: CRS

Symptoms ^{1,*}	• 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. Evaluation for HLH should be considered in patients with severe or unresponsive CRS.
Risk factors for severe CRS ¹	• High pre-infusion tumour burden, active infection and early onset of fever or persistent fever after 24 hours of symptomatic treatment.
Incidence ^{1,*}	• CRS was reported in 83% of patients (n=330); 79% (n=314) of patients had CRS events that were Grade 1 or Grade 2, 4% (n=15) 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=324) recovered from CRS.
Time to onset ^{1,*}	• Time to onset of CRS may vary between CAR-T cell therapies. In clinical studies, the median time from ciltacabtagene autoleucel infusion (Day 1) to onset of CRS was 7 days (range: 1–23 days). Approximately 83% of patients experienced CRS onset after Day 3 of receiving the ciltacabtagene autoleucel infusion.
Duration ^{1,*}	• Median duration of CRS was 4 days (range: 1–18 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-nine percent of patients had a CRS duration of ≤7 days.

*Data from pooled studies (N=396): 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), Phase 2 Study MMY2003 (N=94) and Phase 3 Study MMY3002 (N=196).

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Adverse events: CRS

Monitoring	• Patients should be monitored for signs and symptoms of CRS 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.¹ • Monitoring parameters include: temperature, blood pressure and oxygen saturation.² Patients should be counselled to seek immediate medical attention should signs or symptoms of CRS occur at any time.¹
Grading	• Please refer to your centre's CAR-T cell standard operating procedure 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	• Prior to infusion, the qualified treatment centre must have at least 1 dose of tocilizumab available on-site for use in the event of CRS, with access to an additional dose 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, suitable alternative measures to treat CRS instead of tocilizumab must be available prior to infusion. • 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. • 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 guidance¹

CRS Grade ^a	Tocilizumab ^b	Corticosteroids ^c
Grade 1 Temperature $\geq 38^{\circ}\text{C}^{\text{d}}$	• Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg) may be considered.	• N/A.

^aBased on ASTCT 2019 grading system (Lee et al. 2019), modified to include organ toxicity;

^bRefer to tocilizumab prescribing information for details. Consider alternative measures;

^cContinue corticosteroids use until the event is Grade 1 or less; taper steroids if total corticosteroid exposure is greater than 3 days;

^dAttributed 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 (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.¹

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2. Neelapu SS, et al. Nat Rev Clin Oncol. 2018;15(1)47–62.

Management (continued) ¹	CRS Grade ^a	Tocilizumab ^b	Corticosteroids ^c
	Grade 2 Symptoms require and respond to moderate intervention. Temperature $\geq 38^{\circ}\text{C}^{\text{d}}$ with: Hypotension not requiring vasopressors, and/or, Hypoxia requiring oxygen via cannula ^e or blow-by, or, Grade 2 organ toxicity.	• 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 IV fluids up to 1 litre or increasing supplemental oxygen.	• Consider methylprednisolone 1 mg/kg IV twice daily or dexamethasone (e.g. 10 mg IV every 6 hours).
		• 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.^f • Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.	

^aBased on ASTCT 2019 grading system (Lee et al. 2019), modified to include organ toxicity;

^bRefer to tocilizumab prescribing information for details. Consider alternative measures;

^cContinue corticosteroids use until the event is Grade 1 or less; taper steroids if total corticosteroid exposure is greater than 3 days;

^dAttributed 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 (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;

^eLow-flow nasal cannula is ≤ 6 L/min, and high-flow nasal cannula is >6 L/min;

^fMonoclonal antibodies targeting cytokines (for example, anti-IL1 such as anakinra) may be considered based on institutional practice for unresponsive CRS.¹

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Management (continued) ¹	CRS Grade ^a	Tocilizumab ^b	Corticosteroids ^c
	Grade 3 Symptoms require and respond to aggressive intervention. Temperature $\geq 38^{\circ}\text{C}^{\text{d}}$ with: 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.	• Per Grade 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.^f • Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.	• Administer methylprednisolone 1 mg/kg IV twice daily or dexamethasone (e.g. 10 mg IV every 6 hours).

^aBased on ASTCT 2019 grading system (Lee et al. 2019), modified to include organ toxicity;

^bRefer to tocilizumab prescribing information for details. Consider alternative measures;

^cContinue corticosteroids use until the event is Grade 1 or less; taper steroids if total corticosteroid exposure is greater than 3 days;

^dAttributed 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 (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;

^eLow-flow nasal cannula is ≤ 6 L/min, and high-flow nasal cannula is >6 L/min;

^fMonoclonal antibodies targeting cytokines (for example, anti-IL1 such as anakinra) may be considered based on institutional practice for unresponsive CRS.¹

1. CARVYKTI 3.2 x 10⁶–1.0 x 10⁸ cells dispersion for infusion Summary of Product Characteristics.

Management (continued) ¹	CRS Grade ^a	Tocilizumab ^b	Corticosteroids ^c
	Grade 4 Life-threatening symptoms. Requirements for ventilator support, continuous venovenous haemodialysis (CVVHD). Temperature $\geq 38^{\circ}\text{C}^{\text{d}}$ with: 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).	• Per Grade 2. • After 2 doses of tocilizumab, consider alternative anti-cytokine agents.^e • 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).	• Administer dexamethasone 20 mg IV every 6 hours.

^aBased on ASTCT 2019 grading system (Lee et al. 2019), modified to include organ toxicity;

^bRefer to tocilizumab prescribing information for details. Consider alternative measures;

^cContinue corticosteroids use until the event is Grade 1 or less; taper steroids if total corticosteroid exposure is greater than 3 days;

^dAttributed 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 (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;

^eMonoclonal antibodies targeting cytokines (for example, anti-IL1 such as anakinra) may be considered based on institutional practice for unresponsive CRS.¹

1. CARVYKTI 3.2 x 10⁶–1.0 x 10⁸ cells dispersion for infusion Summary of Product Characteristics.

- Other monoclonal antibodies targeting cytokines (for example, anti-IL1 and/or anti-TNF α), 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.¹
- For patients with high pre-infusion tumour burden, early onset of fever, or persistent fever after 24 hours, early tocilizumab should be considered.¹
- The use of myeloid growth factors, particularly granulocyte-macrophage colony-stimulating factor (GM-CSF), should be avoided during CRS.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.¹

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Adverse events: Neurologic toxicities

- Neurologic toxicities occur frequently following treatment with ciltacabtagene autoleucel and can be fatal or life-threatening.¹
- Neurologic toxicities included immune effector cell-associated neurotoxicity syndrome (ICANS), movement and neurocognitive toxicity (MNT) with signs and symptoms of parkinsonism, Guillain-Barré syndrome (GBS), peripheral neuropathies and cranial nerve palsies.¹
- Neurologic toxicity occurred in 23% of patients (n=90); 6% (n=22) of patients had Grade 3 or Grade 4 neurologic toxicity and 1% (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, eleven patients had fatal outcomes with ongoing neurologic toxicity at the time of death; eight deaths were due to infection (including two deaths in patients with ongoing signs and symptoms of parkinsonism) and one death each due to respiratory failure, cardio-respiratory arrest and intraparenchymal haemorrhage.¹
- Baseline neurologic 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.²
- 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.¹
- 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.¹

1. CARVYKTI 3.2 x 10⁶–1.0 x 10⁸ cells dispersion for infusion Summary of Product Characteristics.

2. Yi Lin et al. Lancet Oncol. 2024; 25: e374–87.

ICANS

Symptoms ^{1,*}	• Symptoms included: aphasia, slow speech, dysgraphia, encephalopathy, depressed level of consciousness and confusional state.
Incidence ^{1,*}	• In the pooled studies (N=396), ICANS occurred in 11% of patients (n=45), with 2% (n=8) experiencing Grade 3 or 4 ICANS and <1% (n=1) Grade 5 ICANS.
Time to onset ^{1,*}	• Patients receiving ciltacabtagene autoleucel may experience fatal or life-threatening ICANS following treatment with ciltacabtagene autoleucel, including before CRS onset, 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: 2–15 days, except for 1 patient with onset at 26 days).
Duration ^{1,*}	• Median duration of ICANS was 3 days (range: 1–29 days, except for 1 patient who had a subsequent fatal outcome at 40 days).
Monitoring ¹	• Patients should be monitored for signs or symptoms of ICANS for four weeks after infusion. Continue to monitor patients for signs and symptoms of neurologic toxicities after recovery from CRS and/or ICANS. • At the first sign of neurologic toxicity including ICANS, neurology evaluation should be considered. Rule out other causes of neurologic symptoms.
Grading	• Please refer to your centre's CAR-T cell standard operating procedure or guidelines in order to grade neurologic toxicity. • The most current grading system for ICANS has been developed by the 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 ¹	• 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 on the following page.

*Data from pooled studies (N=396): 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), Phase 2 Study MMY2003 (N=94) and Phase 3 Study MMY3002 (N=196). 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.

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Management
(continued)¹**Table 2: Guidelines for the 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 IV every 6–12 hours for 2–3 days. • Consider non-sedating, anti-seizure medicines (e.g. levetiracetam) for seizure prophylaxis.
ICANS Grade^a	Corticosteroids
Grade 2 ICE score 3–6 ^b or depressed level of consciousness: awakens to voice.	• Administer dexamethasone^c 10 mg IV 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.

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.

^aASTCT 2019 criteria for grading Neurologic Toxicity (Lee et al. 2019);

^bIf patient is arousable and able to perform ICE assessment, assess:

Orientation (orientation 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
Attention (count backwards from 100 by ten)	1 point

If patient is unarousable and unable to perform ICE assessment (Grade 4 ICANS) = 0 points;

^cAll references to dexamethasone administration are dexamethasone or equivalent.¹

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Management (continued) ¹	ICANS Grade ^a	Corticosteroids
	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 10–20 mg IV every 6 hours. • If no improvement after 48 hours or worsening of neurologic toxicity, escalate dexamethasone^c dose to at least 20 mg IV 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.

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.

^aASTCT 2019 criteria for grading Neurologic Toxicity (Lee et al. 2019);

^bIf patient is arousable and able to perform ICE assessment, assess:

Orientation (orientation 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
Attention (count backwards from 100 by ten)	1 point

If patient is unarousable and unable to perform ICE assessment (Grade 4 ICANS) = 0 points;

^cAll references to dexamethasone administration are dexamethasone or equivalent;

^dIntracranial 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 v5.0.¹

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Management (continued) ¹	ICANS Grade ^a	Corticosteroids
	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^d: • 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 10–20 mg IV 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.

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.

^aASTCT 2019 criteria for grading Neurologic Toxicity (Lee et al. 2019);

^bIf patient is arousable and able to perform ICE assessment, assess:

Orientation (orientation 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
Attention (count backwards from 100 by ten)	1 point

If patient is unarousable and unable to perform ICE assessment (Grade 4 ICANS) = 0 points;

^cAll references to dexamethasone administration are dexamethasone or equivalent.¹

^dTremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.¹

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Movement and neurocognitive toxicity (MNT) with signs and symptoms of parkinsonism

Symptoms ^{1,*}	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.
Incidence ^{1,*}	Of the 90 patients in the pooled studies (N=396) experiencing any neurotoxicity, nine male patients had neurologic toxicity with several signs and symptoms of parkinsonism, distinct from ICANS. The maximum toxicity grades of parkinsonism were: Grade 1 (n=1), Grade 2 (n=2), Grade 3 (n=6).
Time to onset ^{1,*}	The median onset of parkinsonism was 38.0 days (range: 14–914 days) from infusion of ciltacabtagene autoleucel.
Duration ^{1,*}	- One patient (Grade 3) died of neurologic toxicity with ongoing parkinsonism 247 days after administration of ciltacabtagene autoleucel. - Two patients (Grade 2 and Grade 3) with ongoing parkinsonism died of infectious causes 162 and 119 days after administration of ciltacabtagene autoleucel. - One patient recovered (Grade 3). - In the remaining 5 patients, symptoms of parkinsonism were ongoing up to 996 days after administration of ciltacabtagene autoleucel.
Risk factors ^{1,*}	All 9 patients had a history of prior CRS (n=1 Grade 1; n=6 Grade 2; n=1 Grade 3; n=1 Grade 4), while 6 of 9 patients had prior ICANS (n=5 Grade 1; n=1 Grade 3).
Monitoring and management ¹	Patients should be monitored for signs and symptoms of parkinsonism that may be delayed in onset and managed with supportive care measures.

*Data from pooled studies (N=396): 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), Phase 2 Study MMY2003 (N=94) and Phase 3 Study MMY3002 (N=196).
 1. CARVYKTI 3.2 x 10⁶–1.0 x 10⁸ cells dispersion for infusion Summary of Product Characteristics.

Guillain-Barré syndrome (GBS)

Symptoms ^{1,*}	• Symptoms reported include those consistent with Miller-Fisher variant of GBS, motor weakness, speech disturbances, and polyradiculoneuritis.
Incidence ^{1,*}	• In the pooled studies (N=396), one patient was reported to have GBS after treatment with ciltacabtagene autoleucel.
Duration ^{1,*}	• Although GBS symptoms improved after receiving treatment with steroids and IV immunoglobulin (IVIG), the patient died 139 days after administration of ciltacabtagene autoleucel due to encephalopathy post gastroenteritis with ongoing GBS symptoms.
Monitoring ¹	• Patients should be monitored for GBS. Patients presenting with peripheral neuropathy should be evaluated for GBS.
Management ¹	• Treatment with IVIG and escalation to plasmapheresis should be considered, depending on toxicity severity.

Peripheral neuropathy

Incidence ^{1,*}	• In the pooled studies (N=396), 28 patients developed peripheral neuropathy, presenting as sensory, motor, or sensorimotor neuropathies.
Time to onset ^{1,*}	• Median time of onset of symptoms was 58 days (range: 1–914 days)
Duration ^{1,*}	• Median duration of peripheral neuropathies was 142 days (range: 1–1062 days) including those with ongoing neuropathy.
Monitoring ¹	• Patients should be monitored for signs and symptoms of peripheral neuropathies.
Management ¹	• Management with short-course systemic corticosteroids should be considered, depending on the severity and progression of signs and symptoms.

*Data from pooled studies (N=396): 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), Phase 2 Study MMY2003 (N=94) and Phase 3 Study MMY3002 (N=196).

1. CARVYKTI 3.2 x 10⁶–1.0 x 10⁸ cells dispersion for infusion Summary of Product Characteristics.

Cranial nerve palsies

Incidence ^{1,*}	• In the pooled studies (N=396), 27 patients experienced 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 ciltacabtagene autoleucel.
Time to onset ^{1,*}	• Median time to onset was 22 days (range: 17–101 days) following infusion of ciltacabtagene autoleucel.
Duration ^{1,*}	• Median time to resolution was 61 days (range: 1–443 days) following onset of symptoms.
Monitoring ¹	• Patients should be monitored for signs and symptoms of cranial nerve palsies.
Management ¹	• Management with short-course systemic corticosteroids should be considered, depending on the severity and progression of signs and symptoms.

- Reduction of baseline burden of disease with bridging therapy prior to infusion with ciltacabtagene autoleucel in patients with high tumour burden should be considered, 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
- It is advisable that outpatients presenting with neurologic toxicities 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 neurologic toxicities are Grade 3 or higher) could be associated with worse prognostic outcomes.

*Data from pooled studies (N=396): 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), Phase 2 Study MMY2003 (N=94) and Phase 3 Study MMY3002 (N=196).
 1. CARVYKTI 3.2 x 10⁶–1.0 x 10⁸ cells dispersion for infusion Summary of Product Characteristics.

Provision of patient information

It is very important to instruct patients and carers 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), 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).¹
- Effects on the nervous system, symptoms of which can occur days or weeks after infusion, and may initially be subtle:
 - Feeling confused, less alert, disorientated, anxious, memory loss
 - Difficulty speaking or slurred speech
 - Slower movements, changes in handwriting
 - 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

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.¹

If the patient or their carer 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**'.
- Patients/carers should carry the **patient alert card for ciltacabtagene autoleucel** at all times to remind them of the signs and symptoms of CRS and neurologic toxicities that require immediate attention. Counsel the patient to share it with any HCP involved in their treatment.

1. CARVYKTI 3.2 x 10⁶–1.0 x 10⁸ cells dispersion for infusion Summary of Product Characteristics.

Effects on ability to drive and use machines¹

- Ciltacabtagene autoleucel has major influence on the ability to drive and use machines. Due to the potential for neurologic events, patients receiving ciltacabtagene autoleucel are at risk for altered or decreased consciousness or coordination in the 8 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 neurologic symptoms.

Blood, organ, tissue, and cell donation¹

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

Other adverse events

Secondary malignancies including of myeloid and T-cell origin

General ¹	• Patients treated with ciltacabtagene autoleucel may develop secondary malignancies. T-cell malignancies have been reported following treatment of haematological malignancies with a BCMA- or CD19-directed CAR-T cell therapy, including ciltacabtagene autoleucel. T-cell malignancies, including CAR-positive malignancies, have been reported within weeks and up to several years following administration of a CD19- or BCMA-directed CAR-T cell therapy. There have been fatal outcomes. • Myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML), including cases with fatal outcomes, have occurred in patients after ciltacabtagene autoleucel infusion.
Monitoring ¹	• Patients should be monitored life-long for secondary malignancies. In the event a secondary malignancy occurs, the company should be contacted for reporting and to obtain instructions on patient samples to collect for testing of secondary malignancy of T-cell origin. In patients with HIV infection, contact the company for the testing of secondary malignancies, including those of non-T cell origin.

*Data from pooled studies (N=396): 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), Phase 2 Study MMY2003 (N=94) and Phase 3 Study MMY3002 (N=196).
 1. CARVYKTI 3.2 x 10⁶–1.0 x 10⁸ cells dispersion for infusion Summary of Product Characteristics.

Available resources

For the CARVYKTI SmPC:

Refer to CARVYKTI 3.2×10^6 – 1.0×10^8 cells dispersion for infusion Summary of Product Characteristics. Available on www.medicines.ie.

For CAR-T Therapy information from the HSE:

www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/car-t-therapy/

Glossary

AML	Acute myeloid leukaemia
ASTCT	American Society for Transplantation and Cellular Therapies
BCMA	B-cell maturation antigen
BiPAP	Bilevel positive airway pressure
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
CNS	Central nervous system
CPAP	Continuous positive airway pressure
CRS	Cytokine release syndrome
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVVHD	Continuous venovenous haemodialysis
EEG	Electroencephalogram
GBS	Guillain-Barré syndrome
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HCP	Healthcare professional
HIV	Human immunodeficiency virus
HLH	Haemophagocytic lymphohistiocytosis
ICANS	Immune effector cell-associated neurotoxicity syndrome

ICE	Immune Effector Cell-associated Encephalopathy
ICP	Intracranial pressure
IV	Intravenous
IVIG	Intravenous immunoglobulin
MDS	Myelodysplastic syndrome
MNT	Movement and neurocognitive toxicity
MRI	Magnetic resonance imaging
SmPC	Summary of Product Characteristics

Reporting of adverse events

- **CARVYKTI[®]▼ (ciltacabtagene autoleucel). This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information.**
- 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 events via: HPRA Pharmacovigilance, Website: www.hpra.ie. Adverse events should also be reported to Janssen Sciences Ireland UC, a Johnson & Johnson Company, on +44 1494 567447 or at dsafety@its.jnj.com.
- 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 Grading¹

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$
With				
Hypotension	None	Not requiring vasopressors	Requiring a 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 (CPAP), bilevel positive airway pressure (BiPAP), 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 $\geq 38^{\circ}\text{C}$ 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.

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1. Lee DW, et al. Biol Blood Marrow Transplant. 2019;25(4):625–638.

ASTCT ICANS Consensus Grading for Adults¹

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7–9	3–6	0–2	0 (patient is 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 generalised that resolves rapidly or non-convulsive seizures on EEG 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
Elevated 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 generalised 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.

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ICE Score¹

ICE		
Orientation	Orientation to year, month, city, hospital	4 points
Naming	Ability to name 3 objects (e.g. 'Point to clock, pen, button')	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

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This image shows a full page of white paper with horizontal blue or grey ruling lines. The lines are evenly spaced and run across the width of the page, typical of notebook paper. There are no margins, text, or other markings visible.

