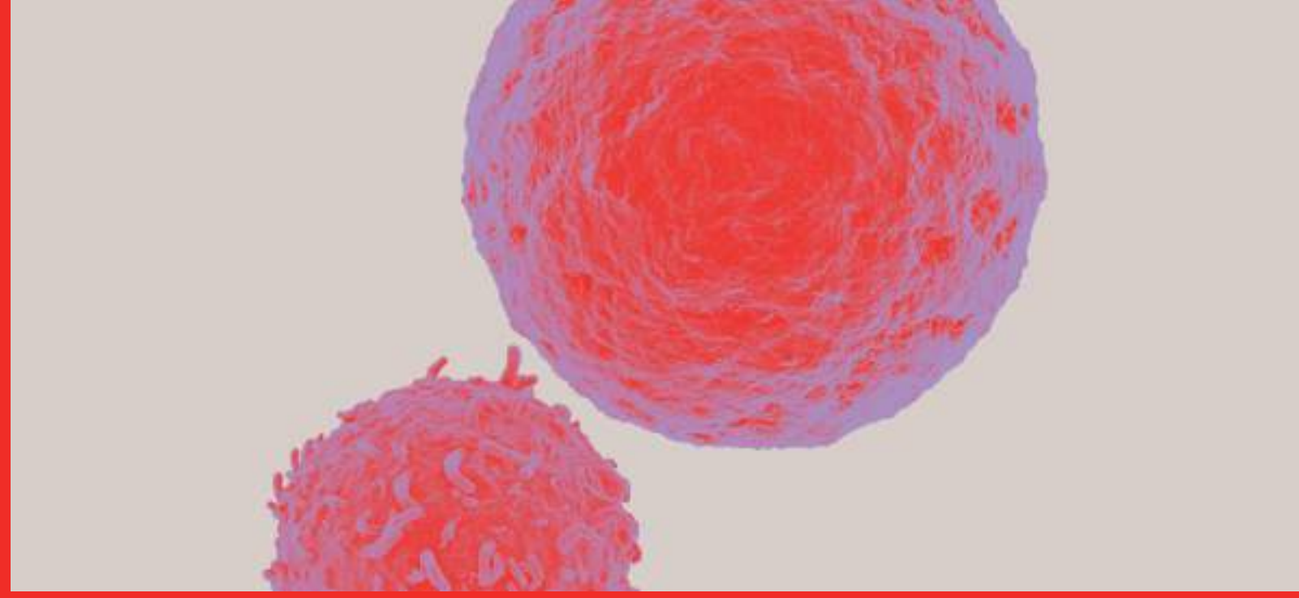

CAR-T Cell Therapy with Ciltacabtagene Autoleucel: Information for CAR-T Centre Healthcare Professionals

Ciltacabtagene autoleucel
CARVYKTI®

For further information please refer to Summary of product characteristics (SPC)

Johnson&Johnson

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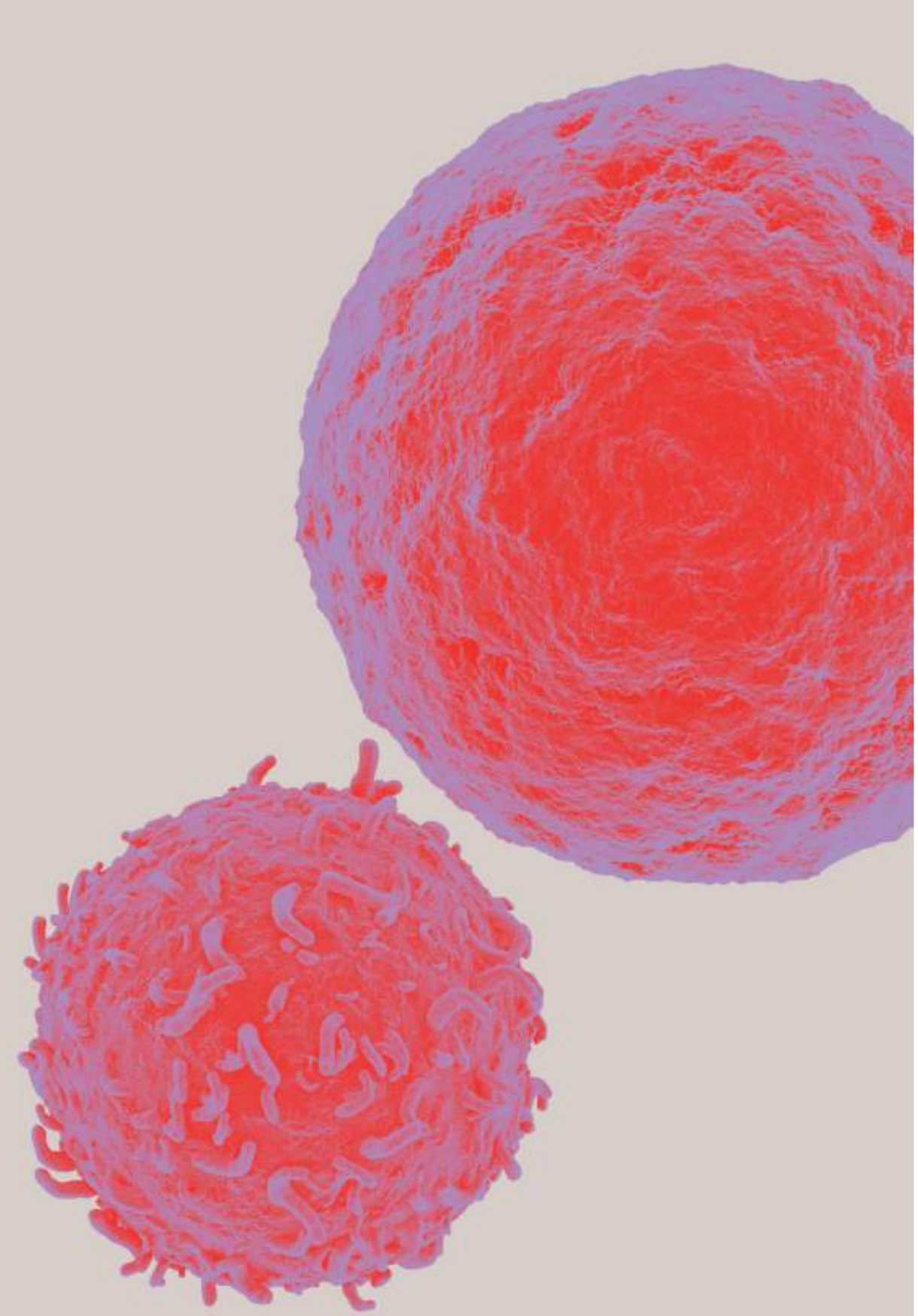

Sections with a light grey background are part of the mandatory Risk Management Plan (RMP) for ciltacabtagene autoleucel

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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]
- After reprogramming, T cells acquire pharmacological activity that gives them the status of drugs.[2]
- 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 professionals (HCPs) on the appropriate management of important selected risks associated with ciltacabtagene autoleucel.

1. CARVYKTI 3.2 x 10^6–1.0 x 10^8 cells dispersion for infusion. Saudi Summary of Product Characteristics, January 2025.
2. Moreno–Martinez ME, et al. Farm Hosp. 2020;44(1):26–31.

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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 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 ciltacabtagene autoleucel Summary of Product Characteristics (SPC), local guidelines or centre-specific protocols for further detail.
  - Efficient interactions between the haematologist, nurse, neurologist, intensive care unit (ICU) specialist, pharmacist, other multidisciplinary team members and the patient/carer.
  - 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.

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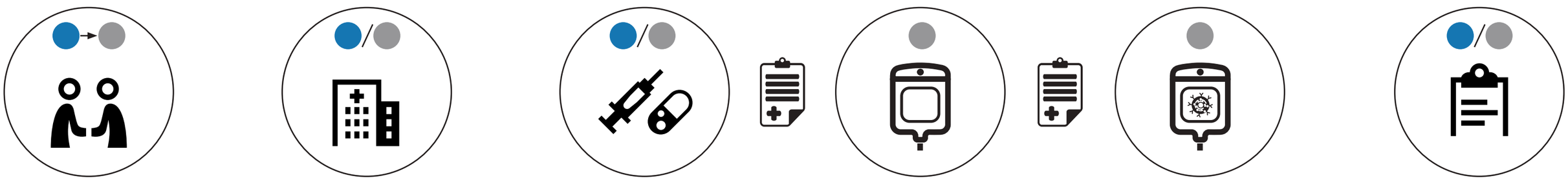
The CAR-T cell therapy process

There are five steps involved in CAR-T cell therapy:[1]



*In the MMY2001 and MMY3002 studies, the median time from the day after receipt of leukapheresis material at the manufacturing facility to release of medicinal product for infusion was **29 days (range: 23–64 days)** and **44 days (range: 25–127 days)**, respectively. The median time from initial leukapheresis to ciltacabtagene autoleucel infusion was **47 days (range: 41–167 days)** and **79 days (range: 45–246 days)**, respectively.

1. CARVYKTI 3.2 x 10^6–1.0 x 10^8 cells dispersion for infusion. Saudi Summary of Product Characteristics, January 2025.

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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 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 the lymphodepleting regimen. 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 human immunodeficiency virus (HIV), active hepatitis B virus (HBV), or active hepatitis C virus (HCV). Screening for HBV, HCV, and HIV and other infectious agents must be performed before collection of cells for manufacturing.[1]
- When considering patients for ciltacabtagene autoleucel treatment, physicians should assess the impact of rapidly progressing disease on the ability of patients to receive CAR-T infusion. Some patients may not benefit from ciltacabtagene autoleucel treatment due to potential increased risk of early death if disease progresses rapidly during bridging therapy.[1]

Leukapheresis

- Leukapheresis involves removing autologous blood mononuclear cells from the patient, after which they will be packaged and sent to the CAR-T cell manufacturing facility. This process can take 3 to 6 hours and may need to be repeated.[1]

1. CARVYKTI 3.2 x 10^6–1.0 x 10^8 cells dispersion for infusion. Saudi Summary of Product Characteristics, January 2025.

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- Please note, patients are required to undergo a wash-out period for certain medications before undergoing leukapheresis. For example, EBMT-JACIE recommendations advise discontinuation of corticosteroids for a minimum of 3 days but ideally 7 days prior to leukapheresis. Please refer to Hayden et al.[1] or local guidelines for further information.

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.[2,3]
- 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.[2] This includes a report on the outcome of bridging therapy, as well as the performance status of the patient and any toxicities experienced.
- Following leukapheresis and prior to administration of ciltacabtagene autoleucel in the MMY2001 study, 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%).[3]

Pre-treatment (lymphodepleting regimen)

- The availability of ciltacabtagene autoleucel should be confirmed prior to starting the lymphodepleting regimen.[3]
- 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).[3]
- A lymphodepleting regimen of cyclophosphamide 300 mg/m^2 intravenous (IV) and fludarabine 30 mg/m^2 IV should be administered daily for 3 days. Ciltacabtagene autoleucel infusion should be administered 5 to 7 days after the start of the lymphodepleting regimen.[3]
- In exceptional cases, the lymphodepleting regimen 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 the lymphodepleting regimen, the performance status of the patient and any toxicities experienced.

1. Hayden PJ, et al. Ann Oncol. 2022;33(3):259–275.
2. Beaupierre A, et al. J Adv Prac Oncol. 2019;10(Suppl 3):29–40.
3. CARVYKTI 3.2 x 10^6–1.0 x 10^8 cells dispersion for infusion. Saudi Summary of Product Characteristics, January 2025.

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- 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.[1,2] 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 lymphodepleting regimen.[3]

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.[3]
- Baseline neurologic 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 appearance of a new neurologic 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/carer-reported outcome measures on quality of life can be useful in addition to neurologic 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. There is no experience of use of ciltacabtagene autoleucel in patients with CNS involvement of myeloma or other pre-existing, clinically relevant CNS illnesses.[3]

1. Cyclophosphamide 500 mg Package Leaflet. 2019.
2. Fludarabine 50 mg Package Leaflet. 2023.
3. CARVYKTI 3.2 x 10^6–1.0 x 10^8 cells dispersion for infusion. Saudi Summary of Product Characteristics, January 2025.

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- 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]

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 only[1] (please refer to the SPC or the ciltacabtagene autoleucel Handling Guide for full details on the handling and preparation of ciltacabtagene autoleucel infusion and the administration process).

1. CARVYKTI 3.2 x 10^6–1.0 x 10^8 cells dispersion for infusion. Saudi Summary of Product Characteristics, January 2025.

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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).
1. CARVYKTI 3.2 x 10^6–1.0 x 10^8 cells dispersion for infusion. Saudi Summary of Product Characteristics, January 2025.

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 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, 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 guidance[1]

CRS Grade[a]	Tocilizumab[b]	Corticosteroids[c]
Grade 1 Temperature ≥38 °C[d]	· Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg) may be considered.	· N/A.

[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; [c]Continue corticosteroids use until the event is Grade 1 or less; taper steroids if total corticosteroid exposure is greater than 3 days; [d]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 (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]
1. CARVYKTI 3.2 x 10^6–1.0 x 10^8 cells dispersion for infusion. Saudi Summary of Product Characteristics, January 2025.
2. Neelapu SS, et al. Nat Rev Clin Oncol. 2018;15(1)47–62.

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Management (continued)[1]	CRS Grade[a]	Tocilizumab[b]	Corticosteroids[c]
	Grade 2 Symptoms require and respond to moderate intervention. Temperature ≥38 °C[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.	

[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; [c]Continue corticosteroids use until the event is Grade 1 or less; taper steroids if total corticosteroid exposure is greater than 3 days; [d]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 (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; [e]Low-flow nasal cannula is ≤6 L/min, and high-flow nasal cannula is >6 L/min; [f]Monoclonal 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 ≥38 °C[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.	• Administer 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). • 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.	

[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; [c]Continue corticosteroids use until the event is Grade 1 or less; taper steroids if total corticosteroid exposure is greater than 3 days; [d]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 (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; [e]Low-flow nasal cannula is ≤6 L/min, and high-flow nasal cannula is >6 L/min; [f]Monoclonal 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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	CRS Grade[a]	Tocilizumab[b]	Corticosteroids[c]
Management (continued)[1]	**Grade 4** Life-threatening symptoms. Requirements for ventilator support, continuous venovenous haemodialysis (CVVHD). Temperature ≥38 °C[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.

[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; [c]Continue corticosteroids use until the event is Grade 1 or less; taper steroids if total corticosteroid exposure is greater than 3 days; [d]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 (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; [e]Monoclonal 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 10^6–1.0 x 10^8 cells dispersion for infusion. Saudi Summary of Product Characteristics, January 2025.

- 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.[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]

1. CARVYKTI 3.2 x 10^6–1.0 x 10^8 cells dispersion for infusion. Saudi Summary of Product Characteristics, January 2025.

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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.
- 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 10^6–1.0 x 10^8 cells dispersion for infusion. Saudi Summary of Product Characteristics, January 2025.

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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.
1. CARVYKTI 3.2 x 10^6–1.0 x 10^8 cells dispersion for infusion. Saudi Summary of Product Characteristics, January 2025.

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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.
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.
[a]ASTCT 2019 criteria for grading Neurologic Toxicity (Lee et al. 2019); [b]If 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; and **Attention** (count backwards from 100 by ten) = 1 point. If patient is unarousable and unable to perform ICE assessment (Grade 4 ICANS) = 0 points; [c]All references to dexamethasone administration are dexamethasone or equivalent.[1]
1. CARVYKTI 3.2 x 10^6–1.0 x 10^8 cells dispersion for infusion. Saudi Summary of Product Characteristics, January 2025.

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.
[a]ASTCT 2019 criteria for grading Neurologic Toxicity (Lee et al. 2019); [b]If 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; and **Attention** (count backwards from 100 by ten) = 1 point. If patient is unarousable and unable to perform ICE assessment (Grade 4 ICANS) = 0 points; [c]All references to dexamethasone administration are dexamethasone or equivalent; [d]Intracranial 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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	ICANS Grade[a]	Corticosteroids
Management (continued)[1]	**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.
[a]ASTCT 2019 criteria for grading Neurologic Toxicity (Lee et al. 2019); [b]If 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; and **Attention** (count backwards from 100 by ten) = 1 point. If patient is unarousable and unable to perform ICE assessment (Grade 4 ICANS) = 0 points; [c]All references to dexamethasone administration are dexamethasone or equivalent;
[d]Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.[1]
1. CARVYKTI 3.2 x 10^6–1.0 x 10^8 cells dispersion for infusion. Saudi Summary of Product Characteristics, January 2025.

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 89 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).
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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).
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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).
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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**', which will explain what to expect at all stages of the CAR-T process.
- Patients/carers should carry the **patient 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.

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Other adverse events

Adverse events: Prolonged and recurrent cytopenias

Incidence[1,*]

	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	191 (48%)	132 (33%)	76 (19%)	14 (4%)
Neutropenia	381 (96%)	111 (28%)	44 (11%)	81 (21%)
Lymphopenia	394 (99%)	97 (25%)	45 (11%)	91 (23%)
Anaemia	184 (47%)	10 (3%)	10 (3%)	26 (7%)

[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 for MMY2001 and MMY2003 or Day 112 for MMY3002, or the start of subsequent therapy, whichever occurs first, 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.
Anaemia: Grade 3 – Hemoglobin <8g/dL. Grade 4 not defined by laboratory count per NCI-CTCAE v5.
Percentages are based on the number of treated patients.

Time to onset[1]	• Most patients had a median time from infusion to first onset of Grade 3 or 4 cytopenia of less than 2 weeks with the majority of patients recovering to Grade 2 or lower by Day 30.
Management and monitoring[1]	• 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 prior to and 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 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 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: Serious infections and febrile neutropenia

Incidence[1,*]	• Infections occurred in 54% of patients (n=213); 18% of patients (n=73) experienced Grade 3 or Grade 4 infections, and fatal infections (COVID-19 pneumonia, pneumonia, sepsis, *Clostridium difficile* colitis, septic shock, bronchopulmonary aspergillosis, pseudomonal sepsis, neutropenic sepsis, and lung abscess) occurred in 4% of patients (n=17). The most frequently reported (≥2%) Grade 3 or higher infections were pneumonia, COVID-19 pneumonia, and sepsis. • Febrile neutropenia was observed in 6% of patients with 2% experiencing serious febrile neutropenia.
Monitoring[1]	• 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[1]	• 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. • Patients treated with ciltacabtagene autoleucel may be at an increased risk of severe/fatal COVID-19 infections. Patients should be counselled on the importance of prevention measures.

Viral reactivation

General[1]	• 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 ciltacabtagene autoleucel 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.

*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: Hypogammaglobulinaemia

Incidence[1,*]	• Hypogammaglobulinaemia may occur in patients receiving ciltacabtagene autoleucel. In the pooled studies (N=396), hypogammaglobulinaemia occurred in 34% of patients, with 5% of patients experiencing Grade 3 hypogammaglobulinaemia. • Laboratory immunoglobulin G (IgG) levels fell below 500 mg/dL after infusion in 91% (360/396) of patients treated with ciltacabtagene autoleucel. • Hypogammaglobulinaemia either as an adverse reaction or a laboratory IgG level below 500 mg/dL occurred in 92% (364/396) of patients after infusion.
Monitoring[1]	• Immunoglobulin levels should be monitored after treatment with ciltacabtagene autoleucel.
Management[1]	• 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 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 to obtain instructions on patient samples to collect for testing.

*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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Hypersensitivity

General[1]	• 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.
Monitoring[1]	• Patients should be carefully monitored for 2 hours after infusion for signs and symptoms of severe reaction.
Management[1]	• Treat promptly and manage patients appropriately according to the severity of the hypersensitivity reaction.

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.

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Additional considerations

COVID-19

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

Effects on ability to drive and use machines[1]

- 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 donation[1]

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

Live vaccines[1]

- The safety of immunisation with live viral vaccines during or following ciltacabtagene autoleucel 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 ciltacabtagene autoleucel treatment, and until immune recovery following treatment with ciltacabtagene autoleucel.

Interference with virological testing[1]

- Due to limited and short spans of identical genetic information between the lentiviral vector used to create ciltacabtagene autoleucel and HIV, some HIV nucleic acid tests may give a false positive result.

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

- Pregnancy status for females of childbearing potential should be verified prior to starting treatment with ciltacabtagene autoleucel.

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- 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 contraception in patients who receive the lymphodepleting chemotherapy.

Pregnancy[1]

- There are no available data on the use of ciltacabtagene autoleucel in pregnant women. 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.

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Available resources

Please refer to Ciltacabtagene autoleucel Saudi SPC for full information on safe use of Ciltacabtagene autoleucel.

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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
DMSO	Dimethyl sulfoxide
EBMT-JACIE	European Society for Blood and Bone Marrow Transplantation-Joint Accreditation Committee ISCT-Europe & EBMT
EEG	Electroencephalogram
GBS	Guillain-Barré syndrome
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HBV	Hepatitis B virus
HCP	Healthcare professional
HCV	Hepatitis C virus
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
IgG	Immunoglobulin G
IV	Intravenous
IVIG	Intravenous immunoglobulin
MDS	Myelodysplastic syndrome
MMSE	Mini Mental State Examination
MNT	Movement and neurocognitive toxicity
MOCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
RMP	Risk management plan
SPC	Summary of Product Characteristics

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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.
- HCPs are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.
- 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.

Adverse events reporting guidance:

- The National Pharmacovigilance Centre (NPC), SFDA:
- Email: npc.drug@sfda.gov.sa
- Telephone: 19999
- Online: http://ade.sfda.gov.sa

For full prescribing information, please refer to the datasheet or contact **Johnson & Johnson Trading Limited (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

Appendix

ASTCT CRS Consensus Grading[1]

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°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 ≥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.

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

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ASTCT ICANS Consensus Grading for Adults[1]

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 Score[1]

	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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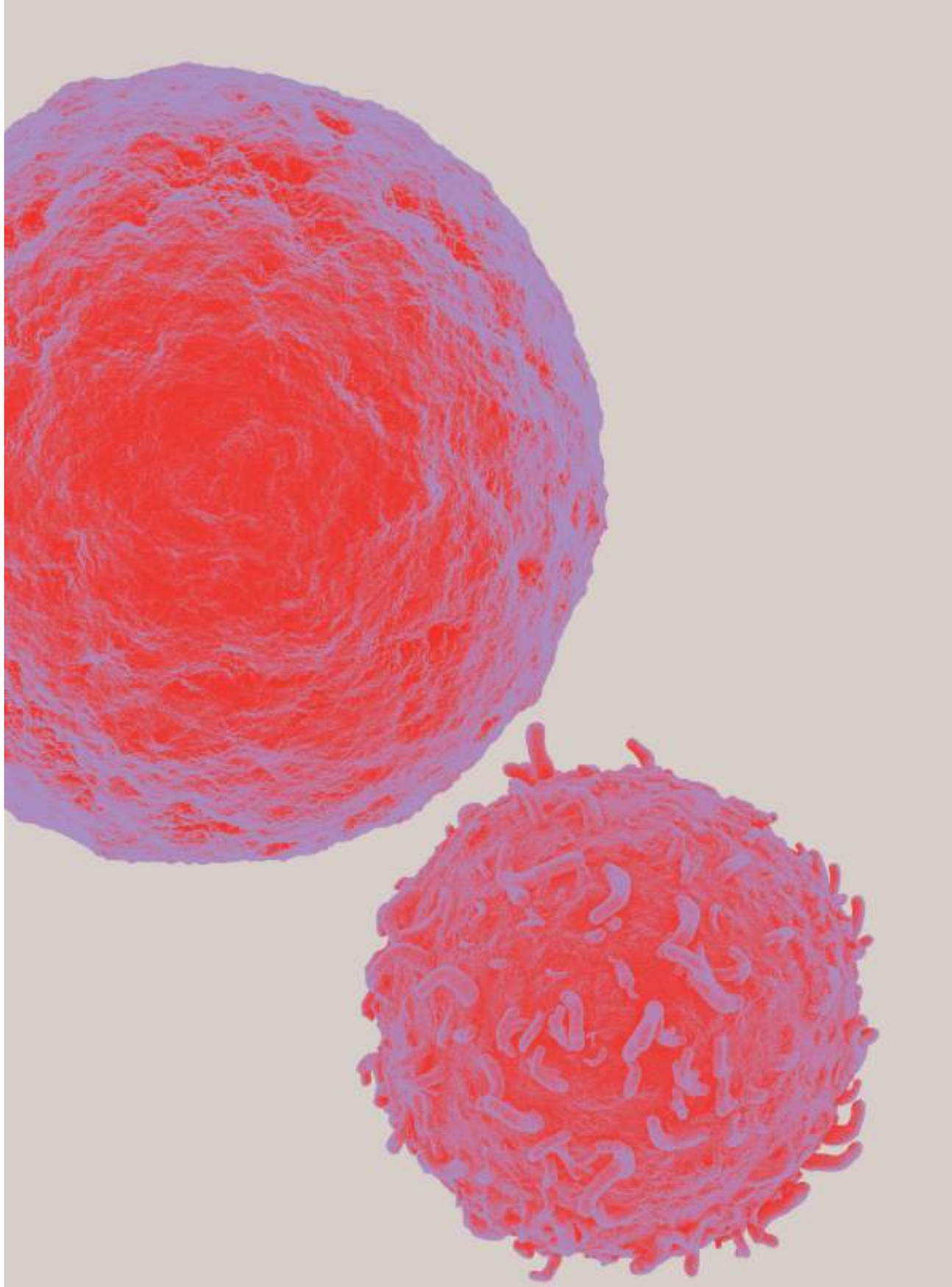
Notes



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Adverse events reporting guidance:

- The National Pharmacovigilance Centre (NPC), SFDA:
- Email: npc.drug@sfda.gov.sa
- Telephone: 19999
- Online: http://ade.sfda.gov.sa

For full prescribing information, please refer to the datasheet or contact **Johnson & Johnson Trading Limited (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