YESCARTA® (axicabtagene ciloleucel) suspension for intravenous infusion

Important safety information for healthcare professionals to minimise the risks of cytokine release syndrome and serious neurologic adverse reactions

YESCARTA® (axicabtagene ciloleucel) Suspension for IV infusion

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADL
Activities of daily living

CAR
Chimeric antigen receptor

CRS
Cytokine release syndrome

CTCAE
Common terminology criteria for adverse events

CVVHD
Continuous veno-venous haemodialysis

DLBCL
Diffuse large B-cell lymphoma

EEG
Electroencephalogram

HCP
Healthcare professional

HLH/MAS
Haemophagocytic lymphohistiocytosis/ macrophage activation syndrome

ICANS
Immune effector cell-associated neurotoxicity syndrome

LBCL
Large B-cell lymphoma

MRI
Magnetic resonance imaging

PAC
Patient Alert Card

PMBCL
Primary mediastinal large B-cell lymphoma

01
Indications

YESCARTA® (axicabtagene ciloleucel) is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of:

LARGE B-CELL LYMPHOMA

- Adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy.

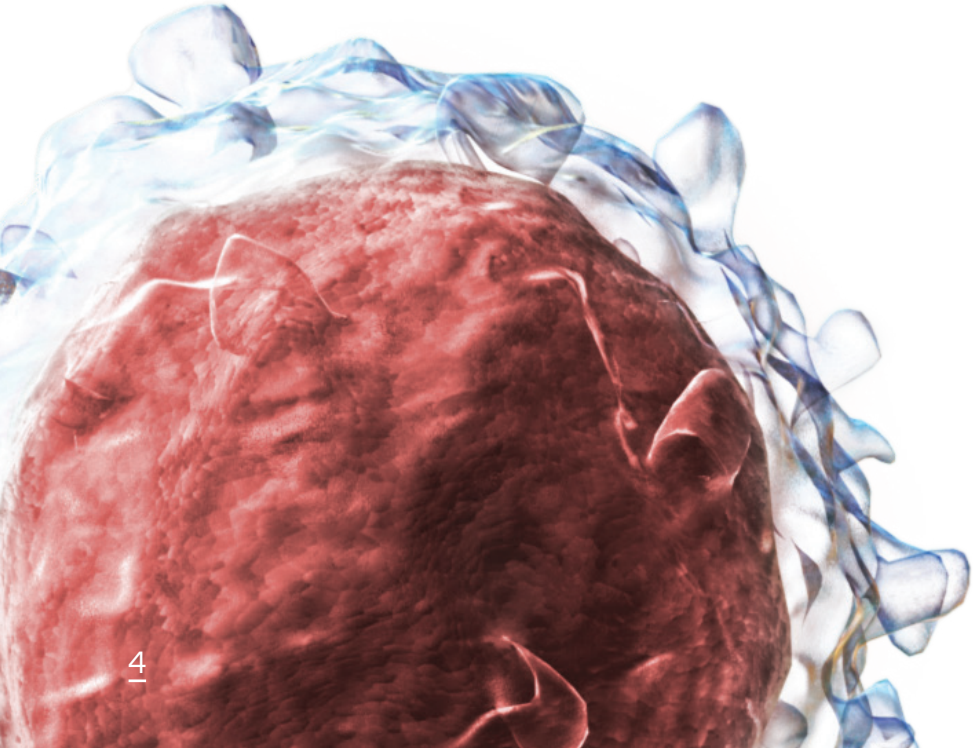
- Adult patients with relapsed or refractory large B-cell lymphoma (LBCL) after two or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma (PMBCL), HGBL, and DLBCL arising from follicular lymphoma.

Limitations of use: YESCARTA® is not indicated for the treatment of patients with primary central nervous system lymphoma.

YESCARTA® administration can result in severe, life-threatening, and fatal reactions like cytokine release syndrome (CRS) and serious neurologic adverse reactions.

YESCARTA® will only be supplied to hospitals and associated centres that are certified and only if the healthcare professionals (HCPs) involved in the treatment of a patient have completed the training programme and have on-site, immediate access to tocilizumab.

To mitigate the safety risks associated with this product, clinical facilities must be specifically certified prior to ordering YESCARTA®.



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Purpose of the educational material for YESCARTA®

This guide is intended to provide information on serious adverse reactions of CRS and serious neurologic adverse reactions/immune effector cell-associated neurotoxicity syndrome (ICANS) associated with YESCARTA®, including guidance on monitoring for CRS and neurologic adverse reactions and reporting of any adverse reactions. The educational material will focus on how to manage symptoms associated with CRS and serious neurologic adverse reactions/ICANS. HCPs are encouraged to report any suspected adverse reactions. All patients or their caregivers must be given a Patient Educational Guide and Patient Alert Card (PAC) by their HCP to educate them about the symptoms of CRS and serious neurologic adverse reactions/ICANS and the need to report the symptoms to their treating doctor immediately. It is advised that patients keep the PACs with them at all times and show it to any HCP who may treat them.

The full Singapore Package Insert and the Patient Information Leaflet for YESCARTA® contain a more detailed description of the risks associated with YESCARTA®. This HCP Educational Material will enable you to understand how YESCARTA® is used and will help you to:

- Identify patients with serious adverse reactions of CRS and serious neurologic adverse reactions/ICANS
- Grade the severity of CRS or serious neurologic adverse reactions/ICANS
- Appropriately manage the adverse reactions of CRS or serious neurologic adverse reactions/ICANS according to the severity grade
- Utilise the Patient Educational Guide and PAC with patients
- Report adverse reactions and facilitate continued monitoring of the product

The information in this guide is provided by KITE, a Gilead Company, (hereafter referred to as Kite) for HCPs who are involved in the treatment of patients who receive YESCARTA®. To obtain copies of the Patient Educational Guide and PAC, contact Kite Medical Information at asiamedinfo@gilead.com. You may refer to the YESCARTA® Singapore Package Insert for more information.

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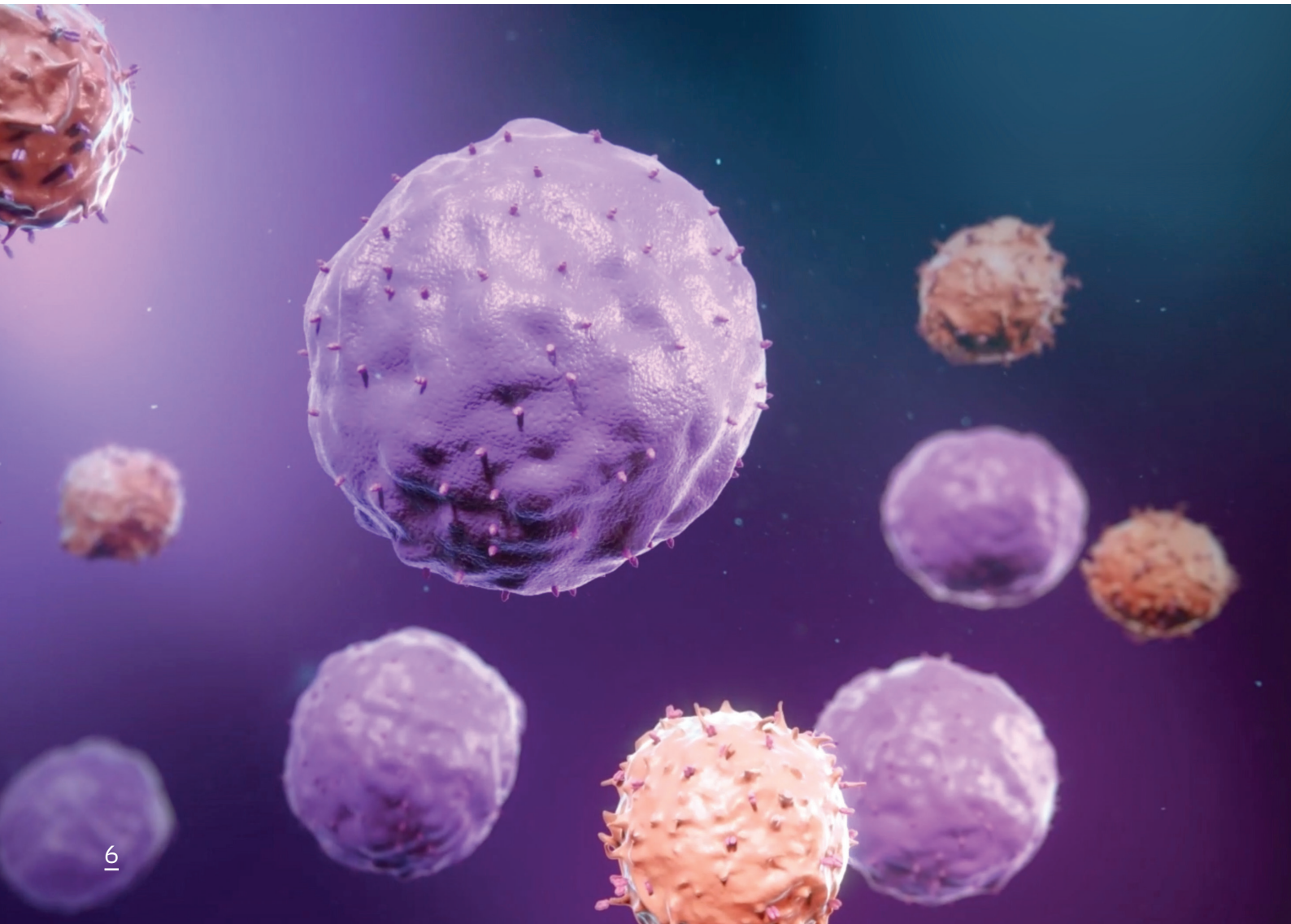
What is YESCARTA®

YESCARTA® is a CD19-directed genetically modified autologous T-cell immunotherapy product that binds to CD19-expressing cancer cells and normal B cells. Following anti-CD19 chimeric antigen receptor (CAR)-T cell engagement with CD19-expressing target cells, the CD28 co-stimulatory domains and CD3-zeta signaling domain activate downstream signaling cascades that lead to T-cell activation, proliferation, acquisition of effector functions, and secretion of inflammatory cytokines and chemokines. This sequence of events leads to killing of CD19-expressing target cells.



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Important points to consider before you administer YESCARTA®

- To mitigate the safety risks associated with YESCARTA®, healthcare facilities must be specifically certified prior to ordering YESCARTA®. As part of the certification process, HCPs will be trained using the educational materials. The treatment centre is responsible for ensuring the training of appropriate personnel.
- YESCARTA® must be administered in a certified healthcare setting. The certified healthcare facility must have on-site, immediate access to tocilizumab (an interleukin-6 receptor inhibitor), and ensure that a minimum of 2 doses of tocilizumab are available for each patient for infusion within 2 hours after YESCARTA® infusion, if required for the treatment of CRS.
- Monitor patients daily for at least 7 days at a certified healthcare facility following YESCARTA® infusion for signs and symptoms of CRS, neurologic adverse reactions and other toxicities. Monitor patients for signs or symptoms of CRS and neurologic toxicities for 4 weeks after infusion and treat promptly.
- Weekly phone calls to the patients by the infusion site HCP for assessments are strongly recommended after the first week of daily monitoring.
- Instruct patients to remain within proximity (within 2 hours of travel) of a certified healthcare facility for at least 4 weeks following infusion.
- Consider the use of prophylactic corticosteroids in patients after weighing the potential benefits and risks. Refer to the Singapore Package Insert for more information.

Due to the risks associated with YESCARTA®, infusion should be delayed if a patient has any of the following conditions:

- Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions or hypotension) including from preceding chemotherapies
- Active uncontrolled infection or inflammatory disease
- Active graft versus host disease

YESCARTA® should not be administered until these conditions have resolved.

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Guidance on managing cytokine release syndrome

Table. 1 | Signs and Symptoms Associated With CRS

CRS

Any organ can be affected by CRS. The following are common signs and symptoms:

Pyrexia	Chills
Tiredness	Renal impairment
Cardiac failure	Headache
Tachycardia	Malaise
Cardiac arrhythmias	Transaminitis
Dyspnoea	Nausea
Hypoxia	Diarrhoea
Capillary leak syndrome	Hypotension

Abbreviations: CRS = cytokine release syndrome.

CRS occurred in 92% (257/278) of patients with LBCL in ZUMA-7 and ZUMA-1. Eight percent (8%) of patients experienced Grade 3 or higher (severe, life threatening and fatal) CRS. In ZUMA-1, the median time to onset of CRS was 2 days (range: 1 to 12 days) and the median duration was 7 days (range: 2 to 29 days, except for one outlier of 58 days). In ZUMA-7, the median time to onset of CRS was 3 days following infusion (range: 1 to 10 days) and the median duration was 7 days (range: 2 to 43 days).

The most common signs and symptoms associated with CRS include pyrexia (93%), hypotension (44%), chills (23%), sinus tachycardia (22%), hypoxia (21%), tachycardia (15%) and headache (14%). Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS).

Monitor patients daily for the first 7 days following YESCARTA® infusion for signs and symptoms of CRS, neurologic adverse reactions/ICANS and other toxicities. Advise patients to remain within proximity (within 2 hours of travel) of a certified clinical facility for at least 4 weeks following infusion, and to seek immediate medical attention should signs or symptoms of CRS occur at any time.

YESCARTA® should not be administered to patients with active infections or inflammatory disease until these conditions have resolved. Diagnosis of CRS requires excluding alternative causes of systemic inflammatory response, including infection. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids and other supportive care as medically indicated.

CRS has been known to be associated with end organ dysfunction (e.g., hepatic, renal, cardiac, and pulmonary). In addition, worsening of underlying organ pathologies can occur in the setting of CRS. Patients with medically significant cardiac dysfunction should be managed by standards of critical care and measures such as echocardiography should be considered. HLH/MAS presents with symptoms similar to CRS. Evaluation for HLH/MAS should be considered in patients with severe or unresponsive CRS.

Patients who experience Grade 2 or higher CRS (e.g., hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive care supportive therapy.

YESCARTA® continues to expand and persist following administration of tocilizumab and corticosteroids. Tumor necrosis factor antagonists are not recommended for the management of CRS associated with YESCARTA®.

Treatment algorithms have been developed to ameliorate some of the CRS symptoms experienced by patients who were treated with YESCARTA® (see Table 3 for more details).

Table 2 describes the grading of CRS according to the Lee criteria*:

Table. 2 | CRS Grading (Excluding Neurologic Adverse Reactions)

Lee Grade	Symptoms
Grade 1	Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise)
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement < 40% FiO2 or Hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement ≥ 40% FiO2 or Hypotension requiring high dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis
Grade 4	Life-threatening symptoms Requirements for ventilator support or CVVDH or Grade 4 organ toxicity (excluding transaminitis)

Abbreviations: CRS = cytokine release syndrome; CVVDH = continuous veno-venous haemodialysis
*Lee et al. 2014.

Table. 3 | Categories of CRS Severity and Management

CRS Grade[a]	Supportive Care	Tocilizumab	Corticosteroids
Grade 1			
• Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	• Supportive care per institutional standard of care. • Closely monitor neurologic status.	• If symptoms (e.g., fever) not improving after 24 hours, consider managing as Grade 2.	• If not improving after 3 days, administer one dose of dexamethasone 10 mg IV.
Grade 2			
• Symptoms require and respond to moderate intervention. • Oxygen requirement < 40% FiO2 or hypotension responsive to fluids or low dose of one vasopressor or • Grade 2 organ toxicity[b].	• Continuous cardiac telemetry and pulse oximetry as indicated. • IV fluids bolus for hypotension with 0.5 to 1.0 L isotonic fluids. • Vasopressor support for hypotension not responsive to IV fluids. • Supplemental oxygen as indicated.	• Administer tocilizumab[c] 8 mg/kg IV over 1 hour (not to exceed 800 mg). • If no clinical improvement in the signs and symptoms of CRS after the first dose, repeat tocilizumab every 8 hours as needed. • Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses. • If improving, discontinue tocilizumab.	• Administer dexamethasone 10 mg IV once daily. • If improving, manage as Grade 1 above and continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate. • If not improving, manage as appropriate grade below.

CRS Grade[a]	Supportive Care	Tocilizumab	Corticosteroids
Grade 3			
• Symptoms require and respond to aggressive intervention. • Oxygen requirement ≥ 40% FiO2 or hypotension requiring high dose or multiple vasopressors or • Grade 3 organ toxicity or Grade 4 transaminitis.	• Management in monitored care or intensive care unit.	• Per Grade 2. • If improving, manage as appropriate grade above.	• Dexamethasone 10 mg IV 3 times a day. • If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate. • If not improving, manage as Grade 4.
Grade 4			
• Life-threatening symptoms. • Requirements for ventilator support or CVVHD or • Grade 4 organ toxicity (excluding transaminitis).	• Per Grade 3. • Mechanical ventilation and/or renal replacement therapy may be required.	• Per Grade 2. • If improving, manage as appropriate grade above.	• Administer methylprednisolone 1000 mg IV once per day for 3 days. • If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. • If not improving, consider methylprednisolone 1000 mg 2–3 times a day or alternate therapy[d]

Abbreviations: CRS = cytokine release syndrome, CVVHD = continuous veno-venous hemodialysis, IV = intravenously.
a. Lee et al. 2014. **b.** Refer to Table 5 for management of neurologic toxicity. **c.** Refer to tocilizumab Package Insert for details.
d. Alternate therapy includes (but is not limited to): anakinra, siltuximab, ruxolitinib, cyclophosphamide, intravenous immunoglobulin and anti-thymocyte globulin.

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Guidance on managing neurologic adverse reactions/ICANS

Table. 4 | Signs and Symptoms Associated With Neurologic Adverse Reactions

Neurologic adverse reactions

The following are common signs and symptoms:

Seizures	Ataxia
Somnolence	Memory impairment
Headache	Mental status changes
Confusion	Hallucinations
Agitation	Depressed level of consciousness
Speech disorders	Delirium
Tremor	Dysmetria
Encephalopathy	

Neurologic toxicities occurred in 62% (173/278) of patients with LBCL. Twenty-five percent (25%) of patients experienced Grade 3 or higher (severe or life threatening) neurologic adverse reactions. In ZUMA-1, the median time to onset for neurologic toxicity was 5 days (range: 1 to 17 days) and the median duration was 13 days. In ZUMA-7, the median time to onset for neurologic toxicity was 5 days (range: 1 to 133 days) and median duration was 14 days. Neurologic toxicities occurred in 98% of patients with LBCL within the first 8 weeks of YESCARTA® infusion and in 87% within the first 7 days. Neurologic events resolved in all but 4 subjects who had ongoing neurologic events at the time of death.

The most common signs and symptoms associated with neurologic adverse reactions included tremor (28%), confusional state (25%), encephalopathy (24%), aphasia (20%), and somnolence (13%). Serious events including leukoencephalopathy and seizures occurred with YESCARTA®. Fatal and serious cases of cerebral oedema and encephalopathy, including late-onset encephalopathy, have occurred in patients treated with YESCARTA®.

Spinal cord oedema, myelitis, quadriplegia, dysphagia, ICANS and status epilepticus were reported, in the context of neurologic toxicity, in the post marketing setting.

Patients who experience Grade 2 or higher neurologic toxicities/ICANS should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive care supportive therapy for severe or life-threatening neurologic toxicities. Treatment algorithms have been developed to ameliorate the neurologic adverse reactions experienced by patients on YESCARTA® (see Table 5 for more details).

Advise patients to remain within proximity (within 2 hours of travel) of a certified clinical facility for at least 4 weeks following infusion to monitor for signs and symptoms of neurologic adverse reactions. Counsel patients to seek immediate medical attention should signs or symptoms of neurologic adverse reactions/ICANS occur at any time.

Table. 5 | Grading and Management of Neurologic Adverse Reactions/ICANS

Neurologic Adverse Reaction (Grading Assessment CTCAE[a] 4.03)	Supportive Care	Concurrent CRS	No concurrent CRS
Grade 1			
Examples include: • Somnolence-mild drowsiness or sleepiness. • Confusion-mild disorientation. • Encephalopathy-mild limiting of ADL. • Dysphasia-not impairing ability to communicate.	• Supportive care per institutional standard of care. • Closely monitor neurologic status. • Consider levetiracetam for seizure prophylaxis.	• Administer tocilizumab per Table 3 for management of Grade 1 CRS. • In addition, administer 1 dose of dexamethasone 10 mg IV. • If not improving after 2 days, repeat dexamethasone 10 mg IV.	• Administer 1 dose of dexamethasone 10 mg IV. • If not improving after 2 days, repeat dexamethasone 10 mg IV.
Grade 2			
Examples include: • Somnolence-moderate, limiting instrumental ADL. • Confusion-moderate disorientation. • Encephalopathy-limiting instrumental ADL. • Dysphasia-moderate impairing ability to communicate spontaneously. • Seizure(s).	• Continuous cardiac telemetry and pulse oximetry as indicated. • Closely monitor neurologic status with serial neuro exams to include fundoscopy and measures of cognition and level of consciousness. Consider neurology consult. • Perform brain imaging (e.g., MRI), EEG, and lumbar puncture (with opening pressure) if no contraindications. • Consider levetiracetam for seizure prophylaxis.	• Administer tocilizumab per Table 3 for management of Grade 2 CRS. • In addition, administer dexamethasone 10 mg IV 4 times a day. • If improving, continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate. • If not improving, manage as appropriate grade below.	• Administer dexamethasone 10 mg IV 4 times a day. • If improving, continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate. • If not improving, manage as appropriate grade below.

Grade 3			
Examples include: • Somnolence-obtundation or stupor. • Confusion-severe disorientation. • Encephalopathy-limiting self-care ADL. • Dysphasia-severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly.	• Per Grade 2 • Management in monitored care or intensive care unit. • Consider levetiracetam for seizure prophylaxis.	• Administer tocilizumab per Table 3 for management of Grade 2 CRS. • In addition, administer methylprednisolone 1000 mg IV once daily. • If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. • If not improving, manage as Grade 4.	• Administer methylprednisolone 1000 mg IV once daily. • If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. • If not improving, manage as Grade 4.
Grade 4			
Examples include: • Life-threatening consequences. • Urgent intervention indicated. • Requirement for mechanical ventilation. • Consider cerebral oedema.	• Per Grade 3 • Mechanical ventilation may be required. • Consider levetiracetam for seizure prophylaxis.	• Administer tocilizumab per Table 3 for management of Grade 2 CRS. • In addition, administer methylprednisolone 1000 mg IV twice per day. • If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. • If not improving, consider 1000 mg of methylprednisolone IV 3 times a day or alternate therapy[b]	• Administer methylprednisolone 1000 mg IV twice per day. • If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. • If not improving, consider 1000 mg of methylprednisolone IV 3 times a day or alternate therapy[b]

Abbreviations: ADL = activities of daily living; CRS = cytokine release syndrome; CTCAE = common terminology criteria for adverse events; EEG = electroencephalogram; ICANS = immune effector cell-associated neurotoxicity syndrome, IV = intravenously; MRI = magnetic resonance imaging.
a. Severity based on Common Terminology Criteria for Adverse Events.
b. Alternate therapy includes (but is not limited to): anakinra, siltuximab, ruxolitinib, cyclophosphamide, intravenous immunoglobulin and antithymocyte globulin.

07

Post YESCARTA® infusion monitoring

Post YESCARTA® infusion recommendations:

- Monitor patients daily for the first 7 days following infusion for signs and symptoms of potential CRS, neurologic adverse reactions and other toxicities.
- Advise patients to stay within proximity (within 2 hours of travel) of the certified healthcare facility so that they can be monitored for signs and symptoms of CRS and neurologic adverse reactions.
- Treating HCPs are strongly recommended to make weekly phone calls to patients to assess for any signs or symptoms suggestive of CRS and neurologic adverse reactions after the first week of daily monitoring.
- If the patients develop any signs or symptoms of CRS or neurologic adverse reaction, instruct them to immediately go to the certified healthcare facility (or nearest hospital if travel is deemed unsafe) for evaluation of hospitalisation and treatment which includes supportive care and use of tocilizumab and/or corticosteroids.

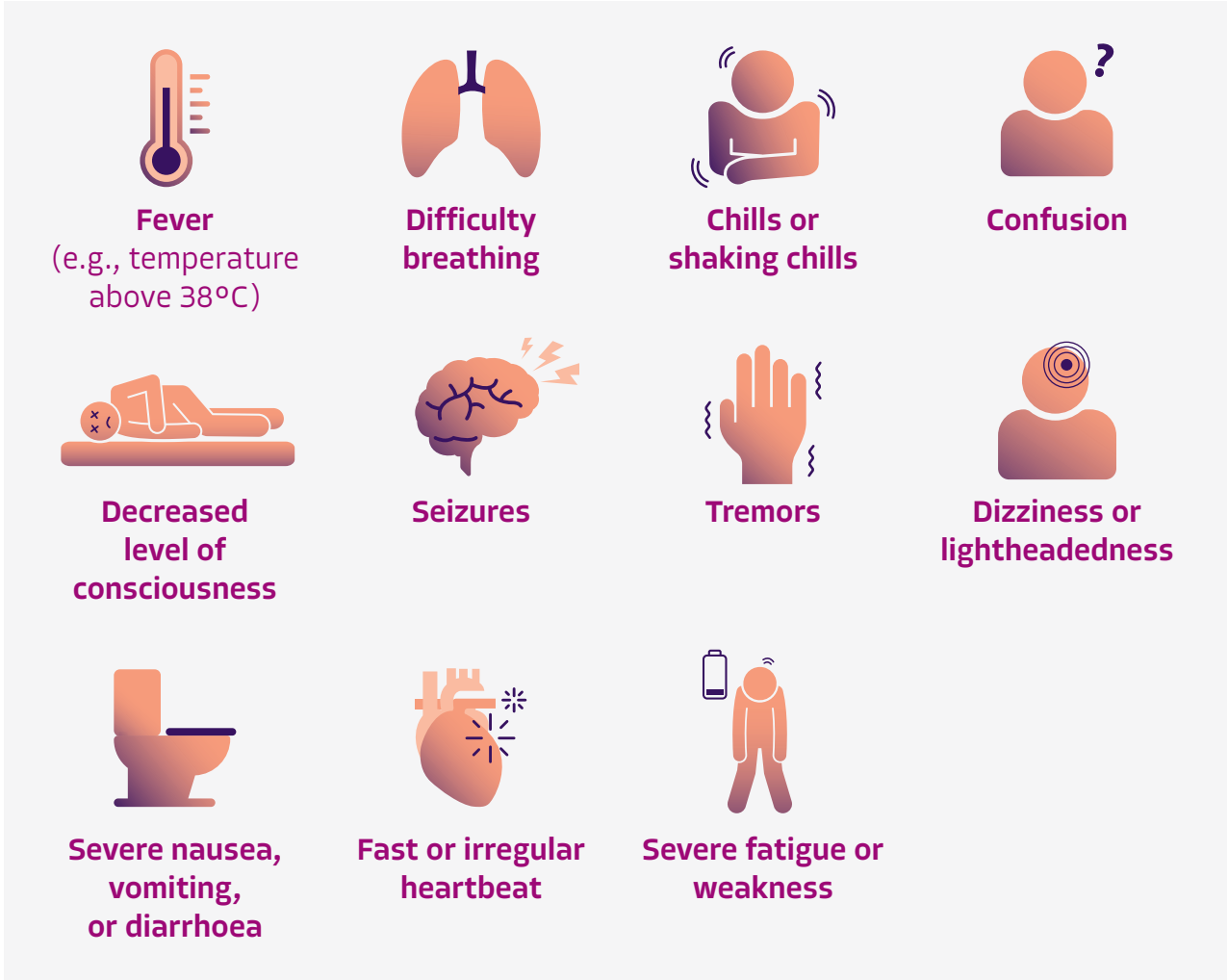
Below is a checklist of some of the signs and symptoms that the HCP can use to assess for during weekly calls to the patient. This checklist is not meant to be all-inclusive. Based on the responses below, the decision to bring the patient for evaluation will be at the discretion of the treating physician.

General	Yes	No
Do you have a fever?	☐	☐
Do you have any chills?	☐	☐
Do you have any nausea or vomiting?	☐	☐
Are you having difficulty sleeping?	☐	☐
Are you having problems staying awake?	☐	☐
Are you lightheaded or experiencing dizziness?	☐	☐
Do you have headaches?	☐	☐
Do you have loss of balance or coordination?	☐	☐
Do you have difficulty in speaking or slurred speech?	☐	☐
Do you have confusion or disorientation?	☐	☐
Do you have any unusual body movements?	☐	☐
Do you have dizziness when you stand up?	☐	☐
Do you have difficulty understanding numbers or doing math?	☐	☐
Do you have difficulty writing?	☐	☐
Do you have shortness of breath or rapid breathing?	☐	☐
Are you having difficulty breathing?	☐	☐
Do you have palpitations?	☐	☐
Are you more tired than you were before the YESCARTA® infusion?	☐	☐

08

Patient counselling

Talk to the patient about the risk of CRS and neurologic adverse reactions. Early diagnosis and appropriate management of CRS and neurologic adverse reactions are essential to minimise life-threatening complications. Remind the patient not to treat their own symptoms. Instruct patients to contact their HCP and/or seek immediate care if they experience any signs and symptoms associated with CRS and/or neurologic adverse reactions, which include:



Provide the YESCARTA® Patient Educational Guide and PAC to the patient or the patient's caregiver. Tell the patient to carry the PAC at all times and to share the PAC with any HCP involved in the patient's treatment.

After YESCARTA® infusion, advise patients to stay within proximity (within 2 hours of travel) of a certified healthcare facility for a minimum of 4 weeks to monitor for signs and symptoms of CRS or neurologic adverse reactions.

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Reporting of adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

HCPs are encouraged to report any suspected adverse reactions associated with YESCARTA® to Safety_FC@gilead.com or the Vigilance and Compliance Branch, Health Products Regulation Group, Health Sciences Authority at Tel: 6866 1111 or report online at https://www.hsa.gov.sg/adverse-events.

In the event that a secondary malignancy of T-cell origin occurs, please contact Kite at asiamedinfo@gilead.com to obtain instructions on the collection of patient samples for testing.

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References

Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124 (2):188-95.

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