Yescarta® ▼ (axicabtagene ciloleucel) Dispersion for infusion

Tecartus® ▼ (brexucabtagene autoleucel) Dispersion for infusion

IMPORTANT SAFETY INFORMATION FOR HEALTHCARE PROFESSIONALS TO MINIMISE THE RISKS OF CYTOKINE RELEASE SYNDROME AND SERIOUS NEUROLOGIC ADVERSE REACTIONS

Yescarta (axicabtagene ciloleucel) is indicated for the treatment of the following:

- 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 DLBCL and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.
- Adult patients with relapsed or refractory follicular lymphoma (FL) after three or more lines of systemic therapy.

Tecartus (brexucabtagene autoleucel) is indicated for the treatment of the following:

- Adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor
- Adult patients 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).

▼ THESE MEDICINAL PRODUCTS ARE SUBJECT TO ADDITIONAL MONITORING. THIS WILL ALLOW QUICK IDENTIFICATION OF NEW SAFETY INFORMATION. HEALTHCARE PROFESSIONALS ARE ASKED TO REPORT ANY SUSPECTED ADVERSE REACTIONS.

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ALL	Acute lymphoblastic leukaemia
BTK	Bruton's tyrosine kinase
CNS	Central nervous system
CRS	Cytokine release syndrome
DLBCL	Diffuse large B-cell lymphoma
FL	Follicular lymphoma
HCP	Healthcare professional
HGBL	High-grade B-cell lymphoma
HLH/MAS	Haemophagocytic lymphohistiocytosis/macrophage activation syndrome
ICANS	Immune effector cell-associated neurotoxicity syndrome
MCL	Mantle Cell Lymphoma
PAC	Patient Alert Card
PMBCL	Primary mediastinal large B-cell lymphoma
SmPC	Summary of Product Characteristics

1. INDICATIONS

Yescarta (axicabtagene ciloleucel) is indicated for the treatment of the following:

- 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 DLBCL and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.
- Adult patients with relapsed or refractory follicular lymphoma (FL) after three or more lines of systemic therapy.

Tecartus (brexucabtagene autoleucel) is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor and for the treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).

The European Commission approved Yescarta (axicabtagene ciloleucel) and Tecartus (brexucabtagene autoleucel) with additional risk minimisation measures for the safe and effective use of these products. Administration of Yescarta or Tecartus can result in severe, life-threatening, and fatal reactions like cytokine release syndrome (CRS) and serious neurologic adverse reactions, also known as immune effector cell-associated neurotoxicity syndrome (ICANS).

Yescarta (axicabtagene ciloleucel) and Tecartus (brexucabtagene autoleucel), hereafter referred to as Kite cellular therapy products, will only be supplied to hospitals and associated centres that are qualified and only if the healthcare professionals (HCPs) involved in the treatment of a patient have completed training on the HCP educational material, and have on-site, immediate access to tocilizumab.
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.

To mitigate the safety risks associated with these two Kite cellular therapy products, treatment centres must be specifically qualified prior to ordering Yescarta or Tecartus.

2. PURPOSE OF THE EDUCATIONAL MATERIAL FOR YESCARTA OR TECARTUS

This guide is intended to provide information on serious adverse reactions of CRS and serious neurologic adverse reactions/ICANS associated with the use of either of these two Kite cellular therapy products, 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 asked to report any suspected adverse reactions. All patients or their caregivers must be given a 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. Treating HCPs should also advise their patients to keep the PACs with them at all times and show it to any HCP who may treat them.

Review the full Summary of Product Characteristics (SmPCs) and the Patient Information Leaflets for Yescarta and/or Tecartus for a more detailed description of these and other risks. Also read this HCP Educational Material prior to prescribing. This will enable you to understand how these two Kite cellular therapy products are used and will help you to:

- Identify and understand serious adverse reactions of CRS and serious neurologic adverse reactions/ICANS
- Appropriately manage the adverse reactions
- Utilise the PAC with patients
- Ensure that adverse reactions are adequately and appropriately reported

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 either of the two Kite cellular therapy products. To obtain copies of the PAC, contact Kite Medical Information at UKMed.Info@gilead.com or by telephone on +353 214825999. Also, see the Yescarta and/or Tecartus SmPCs for more information.

These medicinal products are subject to additional monitoring. This will allow quick identification of new safety information. To report an adverse reaction associated with either of these two Kite cellular therapy products, please email Safety_FC@gilead.com or telephone + 353 (0) 214 825 999.

3. HOW TO USE THIS GUIDE

This guide will help you to:

- Identify patients with CRS or serious neurologic adverse reactions/ICANS
- Learn the importance of excluding alternate causes for the reported symptoms
- Grade the severity of the CRS or serious neurologic adverse reactions/ICANS
- Provide treatment of the CRS or serious neurologic adverse reactions/ICANS according to the severity grade, as shown in this guide

4. WHAT IS YESCARTA OR TECARTUS

Yescarta and Tecartus are engineered autologous T-cell immunotherapy products that bind to CD19-expressing cancer cells and normal B cells. Following anti-CD19 chimeric antigen receptor 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 apoptosis and necrosis of CD19-expressing target cells.

5. IMPORTANT POINTS TO CONSIDER BEFORE YOU ADMINISTER YESCARTA OR TECARTUS

- To mitigate the safety risks associated with these two Kite cellular therapy products, treatment centres must be specifically qualified prior to ordering Yescarta or Tecartus. As a part of the qualification process, HCPs will be trained on the Educational Materials; the treatment centre is responsible for ensuring training of appropriate personnel.
- These two Kite cellular therapy products must be administered in a qualified clinical setting. The qualified treatment centre must ensure the availability of at least 1 dose of tocilizumab (an Interleukin-6 receptor inhibitor) per patient prior to the infusion of Yescarta or Tecartus if required for the treatment of CRS. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensure that suitable alternative measures to treat CRS are available on site.

- Monitor patients daily for the first 10 days following Yescarta or Tecartus infusion for signs and symptoms of CRS, neurologic adverse reactions and other toxicities. Physicians should consider hospitalisation for the first 10 days post Yescarta or Tecartus infusion or at the first signs or symptoms of CRS and/or neurologic events. After the first 10 days following the Yescarta or Tecartus infusion, the patient is to be monitored at the physician's discretion.
- 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 qualified treatment centre for at least 4 weeks following infusion.
- The European Society for Blood and Marrow Transplantation is maintaining a registry for follow-up of patients who received Yescarta or Tecartus. Additional information can be obtained from: **registryhelpdesk@ebmt.org**
  - The aim of the registry is to collect long-term data for Yescarta and Tecartus. Such data is important to further understand the benefit/risk for these products.
  - The inclusion of data in the registry does not replace the obligation to spontaneously report adverse events through **Safety_FC@gilead.com** or telephone + 353 (0) 214 825 999.

Due to the risks associated with these two Kite cellular therapy products, infusion must 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 or Tecartus must not be administered until these conditions have resolved.

6. 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

Yescarta

Safety data described below are from a total of 397 adult patients treated with Yescarta in three multi-centre pivotal clinical studies (ZUMA-1 which treated 108 patients with DLBCL or PMBCL indication; ZUMA-5 which treated 119 patients with FL indication; and ZUMA-7 which treated 170 patients with DLBCL or HGBL indication).

In ZUMA-1 and ZUMA-7, CRS occurred in 92% of patients. Eight percent (8%) of patients experienced Grade 3 or higher (severe, life-threatening, and fatal) CRS. The median time to onset was 3 days (range: 1 to 12 days) and the median duration was 7 days (range: 2 to 58 days). Ninety-nine percent (99%) of patients recovered from CRS.

In ZUMA-5, CRS occurred in 77% of patients. Six percent (6%) of patients experienced Grade 3 or higher (severe, life-threatening, and fatal) CRS. The median time to onset was 4 days (range: 1 to 11 days) and the median duration was 6 days (range: 1 to 27 days). Ninety-nine percent (99%) of patients recovered from CRS.

The most common adverse reactions (≥ 20%) that may be associated with CRS included pyrexia (89%), hypotension (50%), tachycardia (47%), chills (30%), and hypoxia (24%). Serious adverse reactions that may be associated with CRS included pyrexia (12%), hypotension (5%), hypoxia (3%), arrhythmia (3%), cardiac failure (2%), fatigue (2%), headache (2%), tachycardia (2%), cardiac arrest (1%), dyspnoea (1%), and tachypnoea (1%).

Tecartus

Safety data described below are from a total of 182 adult patients treated with Tecartus in two multi-centre pivotal clinical studies (ZUMA-2 which treated 82 patients with MCL indication and ZUMA-3 which treated 100 patients with ALL indication).

CRS occurred in 91% of patients. Twenty percent (20%) of patients experienced Grade 3 or higher (severe or life-threatening) CRS. The median time to onset was 3 days (range: 1 to 13 days) and the median duration (time to resolution) was 9 days (range: 1 to 63 days). Ninety-seven percent (97%) of patients recovered from CRS. The most common signs or symptoms associated with CRS among patients who experienced CRS included pyrexia (94%), hypotension (64%), hypoxia (32%), chills (31%), tachycardia (27%), sinus tachycardia (23%), headache (22%), fatigue (16%) and nausea (13%). Serious adverse reactions that may be associated with CRS included hypotension (22%), pyrexia (15%), hypoxia (9%), tachycardia (3%), dyspnoea (2%) and sinus tachycardia (2%).

Yescarta and Tecartus

Serious adverse reactions that may be associated with CRS include acute kidney injury, atrial fibrillation, ventricular tachycardia, cardiac arrest, cardiac failure, capillary leak syndrome, hypotension, hypoxia, pyrexia, dyspnoea and haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS).

Monitor patients daily for the first 10 days following Yescarta or Tecartus infusion for signs and symptoms of CRS, neurologic adverse reactions and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs or symptoms of CRS and/or neurologic events. After the first 10 days following the infusion, the patient is to be monitored at the physician's discretion. Patients must be instructed to remain within proximity (within 2 hours of travel) of a qualified treatment centre for at least 4 weeks following infusion.

These two Kite cellular therapy products must 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 must be managed by standards of critical care and measures such as echocardiography must be considered. HLH/MAS presents with symptoms similar to CRS. Evaluation for HLH/MAS is to 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) must 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 and Tecartus continue to expand and persist following administration of tocilizumab and corticosteroids. Tumour necrosis factor antagonists are not recommended for management of CRS associated with these two Kite cellular therapy products.

Treatment algorithms have been developed to ameliorate some of the CRS symptoms experienced by patients on either of the two Kite cellular therapy products (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% FiO_2 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% FiO_2 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 CVVHD or Grade 4 organ toxicity (excluding transaminitis)

*Lee D, Gardner R, Porter D, et al. How I treat: current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124(2):188-195.

Abbreviations: CRS = cytokine release syndrome; CVVHD = continuous veno-venous haemodialysis

Table 3. Categories of CRS Severity and Management

CRS Grade[a]	Supportive Care	Tocilizumab[b]	Corticosteroids	Follow-up
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.	N/A.	N/A.	Not improving after 24 hours: • Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).
Grade 2 • Symptoms require and respond to moderate intervention. • Oxygen requirement <40% FiO_2 or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity.	• 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.	• 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 or increasing supplemental oxygen; limit to a maximum of 3 doses in a 24-hour period, maximum total of 4 doses. If no clinical improvement in the signs and symptoms of CRS, or if no response to second or subsequent doses of tocilizumab, consider alternative measures for treatment of CRS. If improving, discontinue tocilizumab.	• If no improvement within 24 hours after starting tocilizumab, manage per Grade 3.	Improving • If corticosteroids were started: continue corticosteroids use until the event is Grade 1 or less, then taper. • Manage as Grade 1 (above). Not improving • Manage as below.
Grade 3 • Symptoms require and respond to aggressive intervention. • Oxygen requirement ≥40% FiO_2 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.	• Methylprednisolone 1 mg/kg IV twice daily or equivalent dexamethasone (e.g., 10 mg IV every 6 hours).	Improving • Continue corticosteroids use until the event is Grade 1 or less, then taper. • Manage as Grade 2 (above). Not improving • Manage as below.
Grade 4 • Life-threatening symptoms. • Requirements for ventilator support or CVVHD. • Grade 4 organ toxicity (excluding transaminitis).	• Per Grade 3. • Mechanical ventilation and/or renal replacement therapy may be required.	• Per Grade 2.	• High-dose corticosteroids: methylprednisolone 1000 mg/day IV for 3 days.	Improving • Continue corticosteroids use until the event is Grade 1 or less, then taper. • Manage as Grade 3 (above) Not improving • Consider adding alternative immunosuppressants.

[a] Lee D, Gardner R, Porter D, et al. How I treat: current concepts in the diagnosis and management of cytokine release syndrome. *Blood*.2014;124(2):188-195. [b] In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, the treatment centre must have access to suitable alternative measures instead of tocilizumab to treat CRS.

Abbreviations: CRS = cytokine release syndrome; CVVHD = continuous veno-venous haemodialysis; IV = intravenous.

7. GUIDANCE ON MANAGING NEUROLOGIC ADVERSE REACTIONS

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	

Yescarta

Safety data described below are from a total of 397 adult patients treated with Yescarta in three multi-centre pivotal clinical studies (ZUMA-1 which treated 108 patients with DLBCL or PMBCL indication; ZUMA-5 which treated 119 patients with FL indication; and ZUMA-7 which treated 170 patients with DLBCL or HGBL indication).

In ZUMA-1 and ZUMA-7, neurologic adverse reactions occurred in 63% of patients. Twenty-five percent (25%) of patients experienced Grade 3 or higher (severe or life-threatening) adverse reactions. Neurologic toxicities occurred within the first 7 days of infusion for 75% of patients. The median time to onset was 6 days (range: 1 to 133 days). The median duration was 10 days, with resolution occurring within 3 weeks for 66% of patients following infusion.

In ZUMA-5, neurologic adverse reactions occurred in 57% of patients. Sixteen percent (16%) of patients experienced Grade 3 or higher (severe or life-threatening) adverse reactions. Neurologic toxicities occurred within the first 7 days of infusion for 65% of patients. The median time to onset was 7 days (range: 1 to 177 days). The median duration was 14 days, with resolution occurring within 3 weeks for 60% of patients following infusion.

The most common (≥ 5%) neurologic adverse reactions included encephalopathy (51%), tremor (28%), and delirium (14%). Serious neurologic adverse reactions reported in patients included encephalopathy (18%), tremor (2%), delirium (2%), hemiparesis (1%) and seizure (1%).

Other neurologic adverse reactions have been reported less frequently in clinical trials and included dysphagia (3%), myelitis (0.2%), and quadriplegia (0.2%).

Adverse reactions reported in the post-marketing setting include status epilepticus (0.3%), spinal cord oedema and ICANS.

Tecartus

Safety data described below are from a total of 182 adult patients treated with Tecartus in two multi-centre pivotal clinical studies (ZUMA-2 which treated 82 patients with MCL indication and ZUMA-3 which treated 100 patients with ALL indication).

Neurologic adverse reactions occurred in 69% of patients. Thirty-two percent (32%) of patients experienced Grade 3 or higher (severe or life-threatening) adverse reactions. The median time to onset was 7 days (range: 1 to 262 days). Neurologic events resolved for 113 out of 125 patients (90.4%) with a median duration of 12 days (range: 1 to 708 days). Three patients had ongoing neurologic events at the time of death, including one patient with the reported event of serious encephalopathy and another patient with the reported event of serious confusional state. The remaining unresolved neurologic events were Grade 2. Ninety-three percent (93%) of all treated patients experienced the first CRS or neurological event within the first 7 days after Tecartus infusion.

The most common neurologic adverse reactions that have been reported in patients administered Tecartus included tremor (32%), confusional state (27%), encephalopathy (27%), aphasia (21%) and agitation (11%). ICANS was reported as a serious adverse neurologic reaction at a low frequency (2%) in clinical trials. ICANS observed during clinical studies are represented under the adverse reaction encephalopathy. Serious cases of cerebral oedema which may become fatal have occurred in patients treated with Tecartus.

ICANS was reported in the context of neurologic toxicity in the post-marketing setting.

Yescarta and Tecartus

There is limited experience with Yescarta and Tecartus in patients with lymphomas involving the central nervous system (CNS). Patients with a history of CNS disorders such as seizures or cerebrovascular ischaemia may be at increased risk. Patients must be monitored at least daily for 10 days at the qualified treatment centre following infusion for signs and symptoms of neurologic toxicity/ICANS. After the first 10 days following the infusion, the patient is to be monitored at the physician's discretion.

Patients who experience Grade 2 or higher neurologic toxicities must 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 either of the two Kite cellular therapy products (see Table 5 for more details). Patients must be instructed to remain within proximity (within 2 hours of travel) of a qualified treatment centre 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 toxicity/ICANS occur at any time.

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

Neurologic Adverse Reaction (Grading Assessment CTCAE 4.03)	Supportive Care	Concurrent CRS[c]	No Concurrent CRS[d]	Follow-up
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 prophylactic non-sedating, antiseizure medication e.g., levetiracetam.	N/A.	N/A.	Not improving • Continue supportive care.
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 prophylactic non-sedating, antiseizure medication e.g., levetiracetam.	• 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 or increasing supplemental oxygen; maximum of 3 doses in a 24-hour period. Maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS. • If no improvement within 24 hours after starting tocilizumab, administer dexamethasone[a] 10 mg IV every 6 hours.[a] If improving, discontinue tocilizumab.	• Dexamethasone at 10 mg IV every 6 hours.	Improving • Continue dexamethasone use until the event is Grade 1 or less, then taper. • Manage as Grade 1 (above). Not improving • Manage as below.

Table 5. Grading and Management of Neurologic Adverse Reactions (continued)

Neurologic Adverse Reaction (Grading Assessment CTCAE 4.03)	Supportive Care	Concurrent CRS[c]	No Concurrent CRS[d]	Follow-up
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.	• Administer tocilizumab per Grade 2. • In addition, administer dexamethasone 10 mg IV every 6 hours.[a]	• Dexamethasone at 10 mg IV every 6 hours.[a]	Improving • Continue dexamethasone use until the event is Grade 1 or less, then taper. • Manage as Grade 2 (above). Not improving • Manage as below.
Grade 4 • Life-threatening consequences. • Urgent intervention indicated. • Requirement for mechanical ventilation. • Consider cerebral oedema.	• Per Grade 3. • Mechanical ventilation may be required.	• Administer tocilizumab per Grade 2. • In addition, administer methylprednisolone[b] 1000 mg/day IV for 3 days.	• Administer methylprednisolone[b] 1000 mg/day IV for 3 days.	Improving • Continue methylprednisolone use until the event is Grade 1 or less, then taper. • Manage as Grade 3 (above). Not improving • Consider alternative immuno-suppressants.

[a]Or equivalent methylprednisolone dose (1 mg/kg).

[b]Equivalent dose of dexamethasone is 188 mg/day.

[c]In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, the treatment centre must have access to suitable alternative measures instead of tocilizumab to treat CRS.

[d]No concurrent CRS: Tocilizumab not indicated.

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 = intravenous; MRI = magnetic resonance imaging.

8. POST YESCARTA OR TECARTUS INFUSION MONITORING

Post Yescarta or Tecartus infusion recommendations:

- Patients must be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurologic adverse reactions and other toxicities.
- Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs or symptoms of CRS and/or neurologic adverse reactions.
- Patients must be instructed to stay within proximity (within 2 hours of travel) of the qualified treatment centre so that they can be monitored for signs and symptoms of CRS and neurologic adverse reactions.
- Treating HCPs should make weekly phone calls to assess for any signs or symptoms suggestive of CRS and neurologic adverse reactions.
- If the patients develop any signs or symptoms of CRS or neurologic adverse reactions, they should be instructed to immediately go to the qualified treatment centre (or nearest hospital if travel is deemed unsafe) for evaluation for hospitalisation and treatment which includes supportive care and use of tocilizumab and/or corticosteroids.

The treating healthcare professional must complete the PAC including the name of the product infused.

Below is a checklist of some of the signs and symptoms that the HCP should 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 maths?		
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 or Tecartus infusion?		

9. 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:

- Fever (e.g., temperature above 38°C)
- Difficulty breathing
- Chills or shaking chills
- Confusion
- Decreased level of consciousness
- Seizures
- Tremors
- Dizziness or lightheadedness
- Severe nausea, vomiting, or diarrhoea
- Fast or irregular heartbeat
- Severe fatigue or weakness

Provide the Yescarta and Tecartus 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 or Tecartus infusion, advise patients to stay within proximity (within 2 hours of travel) of a qualified treatment centre for a minimum of 4 weeks to monitor for signs and symptoms of CRS or neurologic adverse reactions.

10. 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 asked to report any suspected adverse reactions associated with Yescarta or Tecartus to the Marketing Authorisation Holder Kite Pharma EU B.V., a Gilead company, or the Health Products Regulatory Authority (HPRA) via HPRA Pharmacovigilance, website: **www.hpra.ie** in addition to any recording of data in the Cell Therapy Registry.

Any suspected adverse reactions to Yescarta or Tecartus should be reported to Gilead via email to **Safety_FC@gilead.com** or by telephone + 353 (0) 214 825 999.

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.

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Kite
A GILEAD Company