YESCARTA®
(axicabtagene ciloleucel) Dispersion for infusion

TECARTUS®
(brexucabtagene autoleucel) Dispersion for infusion

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ALL	Acute lymphoblastic leukemia
BTK	Bruton's tyrosine kinase
CRS	Cytokine release syndrome
DLBCL	Diffuse large B-cell lymphoma
FL	Follicular lymphoma
HCP	Healthcare provider
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
PI	Prescribing information
PMBCL	Primary Mediastinal Large B-cell lymphoma

1. INDICATIONS

Yescarta is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

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

Limitation of use: Yescarta is not indicated for the treatment of patients with primary or secondary central nervous system (CNS) lymphoma. Yescarta is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

Tecartus 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 unless ineligible to BTK inhibitor.

Tecartus is indicated for the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

Limitation of use: Tecartus is not indicated for the treatment of patients with active CNS lymphoma.

2. PURPOSE OF THE EDUCATIONAL MATERIAL

This guide is intended to provide information on serious adverse reactions of cytokine release syndrome (CRS) and serious neurologic adverse reactions, also known as immune effector cell associated neurotoxicity syndrome (ICANS) associated with the use of Yescarta and Tecartus, including guidance on monitoring for CRS, neurologic adverse reactions, and reporting of any adverse reactions. Other adverse reactions include infections and febrile neutropenia, prolonged cytopenias and hypogammaglobulinemia. The educational material will focus on how to manage symptoms associated with CRS and serious neurologic adverse reactions. Healthcare providers (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 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 Prescribing Information (PI) and the Patient Information Leaflet (PIL) 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 Yescarta and/or Tecartus are used and will help you to:

- Identify and understand serious adverse reactions of CRS and serious neurologic adverse reactions as well as infections and febrile neutropenia, prolonged cytopenias and hypogammaglobulinemia
- Appropriately manage the adverse reactions
- Utilize the PAC with patients
- Ensure that adverse reactions are adequately and appropriately reported

The information in this guide is provided by Gilead Sciences Israel Ltd, for HCPs who are involved in the treatment of patients who receive Yescarta or Tecartus. To obtain copies of the PAC, contact Gilead Medical Information at medinfo.israel@gilead.com. Also, see the Yescarta and/or Tecartus PI 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 Yescarta or Tecartus, please contact the Ministry of Health using the link https://sideeffects.health.gov.il or through the registration holder: Safety_FC@gilead.com.

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 ARE YESCARTA AND 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 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 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 Yescarta or Tecartus treatment, clinical facilities must be specifically qualified prior to ordering Yescarta or Tecartus. As part of the qualification process, HCPs will be trained on the Educational Materials; the treatment center is responsible for ensuring training of appropriate personnel.
- Yescarta and Tecartus must be administered in a qualified clinical setting. The qualified clinical facility 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, for administration within two hours, if required for the treatment of CRS. The treatment center should 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 Israeli Ministry of Health shortage list, 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 hospitalization 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 Yescarta or Tecartus infusion, the patient should 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, no more than 2 hours away, of a qualified clinical facility for at least 4 weeks following infusion.

Due to the risks associated with Yescarta or Tecartus treatment, 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 (GvHD)

Yescarta and Tecartus should not be administered until these conditions have resolved.

6. GUIDANCE ON MANAGING CYTOKINE RELEASE SYNDROME

Table 1. Signs and Symptoms Associated with CRS

CYTOKINE RELEASE SYNDROME	
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
Dyspnea	Nausea
Hypoxia	Diarrhea
Capillary leak syndrome	Hypotension

Abbreviations: CRS = cytokine release syndrome.

6.1 Yescarta

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%) dyspnea (1%) and tachypnoea (1%).

6.2 Tecartus

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 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 the 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%), dyspnea (2%) and sinus tachycardia (2%).

6.2.1 Yescarta and Tecartus

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 hospitalization 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 should be monitored at the physician's discretion. Patients should be instructed to remain within proximity, no more than 2 hours away, of a qualified clinical facility for at least 4 weeks following infusion.

Yescarta and Tecartus 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. Cytokine release syndrome 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. Hemophagocytic lymphohistiocytosis/macrophage activation syndrome (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.

The administration of tocilizumab and/or corticosteroids resulted in a higher anti-CD19 CAR T cell levels for both Yescarta and Tecartus. Tumor necrosis factor (TNF) antagonists are not recommended for management of Yescarta and Tecartus associated CRS. Treatment algorithms have been developed to ameliorate some of the CRS symptoms experienced by patients on Yescarta or Tecartus (see Table 3 for Yescarta and Table 4 for Tecartus 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)

Abbreviations: CRS = cytokine release syndrome; CVVDH = continuous veno-venous haemodialysis; FiO_2 = fraction of inspired oxygen.

*{Lee 2014}

Table 3. Yescarta: 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: • Manage as below
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 treatment per local medical guidance • 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 no improvement within 24 hours after starting tocilizumab, manage per Grade 3	Improving • Manage as above • If corticosteroids were started: continue corticosteroids use until the event is Grade 1 or less, then taper 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 BID or equivalent dexamethasone (e.g., 10 mg IV every 6 hours)	Improving • Manage as above • Continue corticosteroids use until the event is Grade 1 or less, then taper 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	• Methylprednisolone 1000 mg/day IV x 3 days	Improving • Manage as above • Continue corticosteroids use until the event is Grade 1 or less, then taper Not improving • Consider adding alternate immunosuppressants

Abbreviations: BID = twice a day; CRS = cytokine release syndrome; CVVHD = continuous veno-venous haemodialysis; FiO2 = fraction of inspired oxygen; IV = intravenously.

a {Lee 2014}

b In the exceptional case where tocilizumab is not available due to a shortage that is listed in the Israeli Ministry of Health shortage list, ensure that suitable alternative measures to treat CRS are available on site.

Table 4. Tecartus: 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	If not improving after 24 hours, administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg)	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 • If improving, taper corticosteroids, and manage as Grade 1	Improving • Manage as above • If corticosteroids were started: continue corticosteroids use until the event is Grade 1 or less, then taper 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 BID or equivalent dexamethasone (e.g., 10 mg IV every 6 hours)	Improving • Manage as above • Continue corticosteroids use until the event is Grade 1 or less, then taper 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	• Methylprednisolone 1000 mg/day IV x 3 days	Improving • Manage as above • Continue corticosteroids use until the event is Grade 1 or less, then taper Not improving • Consider adding alternate immunosuppressants

Abbreviations: BID = twice a day; CRS = cytokine release syndrome; CVVHD = continuous veno-venous haemodialysis; FiO_2 = fraction of inspired oxygen; IV = intravenously.

a {Lee 2014}

b In the exceptional case where tocilizumab is not available due to a shortage that is listed in the Israeli Ministry of Health shortage list, ensure that suitable alternative measures to treat CRS are available on site.

7. GUIDANCE ON MANAGING NEUROLOGIC ADVERSE REACTIONS

Table 5. 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	

7.1 Yescarta

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%). In ZUMA-7, encephalopathy and tremor were reported in 49% and 25% of patients treated with Yescarta.

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.

7.2 Tecartus

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 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 included tremor (32%), confusional state (27%), encephalopathy (27%), aphasia (21%), and agitation (11%). Serious adverse reactions including encephalopathy (15%), aphasia (6%) and confusional state (5%) have been reported in patients administered Tecartus. 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.

There is limited experience with Yescarta and Tecartus in patients with lymphomas involving the CNS. Patients with a history of CNS disorders such as seizures or cerebrovascular ischemia may be at increased risk.

Patients should be monitored at least daily for 10 days at the qualified clinical facility following infusion for signs and symptoms of neurologic toxicity. After the first 10 days following the infusion, the patient should be monitored at the physician's discretion.

Patients who experience Grade 2 or higher neurologic toxicities 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 or Tecartus (see Table 6 for Yescarta and Table 7 for Tecartus for more details). Patients should be instructed to remain within proximity, no more than 2 hours away, of a qualified 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 occur at any time.

Table 6. Yescarta: Grading and Management of Neurologic Adverse Reactions

Neurologic Adverse Reaction (Grading Assessment CTCAE 4.03)	Supportive Care	Concurrent CRS[d]	No Concurrent CRS[c]	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	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. As required, consider including fundoscopy and measures of cognition and level of consciousness • As required, consider performing 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; 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 • If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg IV every 6 hours[a]	• Dexamethasone at 10 mg IV every 6 hours	Improving • Manage as above • Continue dexamethasone use until the event is Grade 1 or less, then taper Not improving • Manage as below

Table 6. Yescarta: Grading and Management of Neurologic Adverse Reactions (continued)

Neurologic Adverse Reaction (Grading Assessment CTCAE 4.03)	Supportive Care	Concurrent CRS[d]	No Concurrent CRS[c]	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[a] 10 mg IV with the first dose of tocilizumab and repeat dose every 6 hours	• Dexamethasone at 10 mg IV every 6 hours[a]	Improving • Manage as above • Continue dexamethasone use until the event is Grade 1 or less, then taper 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 IV per day with first dose of tocilizumab and continue with methylprednisolone 1000 mg intravenously per day for 2 more days	• Administer methylprednisolone[b] 1000 mg/day IV x 3 days	Improving • Continue methylprednisolone use until the event is Grade 1 or less, then taper over 3 days Not improving • Consider 1000 mg of methylprednisolone intravenously 3 times a day or alternate therapy[e]

Abbreviations: ADL = activities of daily living; CRS = cytokine release syndrome; CTCAE = common terminology criteria for adverse events; EEG = Electroencephalogram; IV = intravenously; MRI = magnetic resonance imaging.

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

b Equivalent dose of dexamethasone is 188 mg/day.

c No concurrent CRS: Tocilizumab not indicated.

d In the exceptional case where tocilizumab is not available due to a shortage that is listed in the Israeli Ministry of Health shortage list, ensure that suitable alternative measures to treat CRS are available on site.

e Alternate therapy includes (but is not limited to): anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG and ATG

Table 7. Tecartus: Grading and Management of Neurologic Adverse Reactions

Neurologic Adverse Reaction (Grading Assessment CTCAE 4.03)	Supportive Care	Concurrent CRS[d]	No Concurrent CRS[c]	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 nonsedating, 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. As required, consider including fundoscopy and measures of cognition and level of consciousness. Consider neurology consult • As required, consider performing 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; 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. If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg IV every 6 hours[a]. If improving, discontinue tocilizumab	• Dexamethasone at 10 mg IV every 6 hours	Improving • Manage as above • Discontinue tocilizumab • Continue dexamethasone use until the event is Grade 1 or less, then taper. Not improving • Manage as 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 non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis	• Administer tocilizumab per Grade 2 • In addition, administer dexamethasone[a] 10 mg IV with the first dose of tocilizumab and repeat dose every 6 hours. If improving, discontinue tocilizumab	• Dexamethasone at 10 mg IV every 6 hours[a]	Improving • Manage as above • Continue dexamethasone use until the event is Grade 1 or less, then taper Not improving • Manage as below

Table 7. Tecartus: Grading and Management of Neurologic Adverse Reactions (continued)

Neurologic Adverse Reaction (Grading Assessment CTCAE 4.03)	Supportive Care	Concurrent CRS[d]	No Concurrent CRS[c]	Follow-up
Grade 4 • Life-threatening consequences • Urgent intervention indicated • Requirement for mechanical ventilation • Consider cerebral oedema	• Per Grade 3 • Mechanical ventilation may be required • Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis	• Administer tocilizumab per Grade 2 • In addition, administer methylprednisolone[b] 1000 mg IV per day with first dose of tocilizumab and continue with methylprednisolone 1000 mg intravenously per day for 2 more days	• Administer methylprednisolone[b] 1000 mg/day IV x 3 days	Improving • Continue methylprednisolone use until the event is Grade 1 or less, then taper Not improving • Consider alternate immunosuppressants

Abbreviations: ADL = activities of daily living; CRS = cytokine release syndrome; CTCAE = common terminology criteria for adverse events; EEG = Electroencephalogram; IV = intravenously; MRI = magnetic resonance imaging.

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

b Equivalent dose of dexamethasone is 188 mg/day.

c No concurrent CRS: Tocilizumab not indicated.

In the exceptional case where tocilizumab is not available due to a shortage that is listed in the Israeli Ministry of Health shortage list, ensure that suitable alternative measures to treat CRS are available on site.

* Consider seizure prophylaxis in patients at higher risk of seizure, such as those with prior seizure history, CNS disease, concerning EEG findings, or neoplastic brain legions {Neelapu 2018, Yakoub-Agha 2020}.

8. INFECTIONS AND FEBRILE NEUTROPENIA

8.1 Yescarta

Febrile neutropenia was observed in 10% of patients after Yescarta infusion. Infections occurred in 48% of patients. Grade 3 or higher (severe, life-threatening, or fatal) infections occurred in 19% of patients. Grade 3 or higher unspecified pathogen, bacterial, and viral infections occurred in 12%, 6%, and 5% of patients respectively. The most common site of unspecified pathogen infection was in the respiratory tract. In ZUMA-7, febrile neutropenia and viral infection were reported in 2% and 16% of patients treated with Yescarta.

8.1.1 Monitoring and management guidance

Serious infections have been very commonly observed with Yescarta. Patients should be monitored for signs and symptoms of infection before, during, and after Yescarta infusion and treated appropriately. Prophylactic anti microbials should be administered according to standard institutional guidelines. Febrile neutropenia has been observed in patients after Yescarta infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated.

8.2 Tecartus

Febrile neutropenia was observed in 12% of patients after Tecartus infusion. Infections occurred in 87 of the 182 patients treated with Tecartus in ZUMA-2 and ZUMA-3. Grade 3 or higher (severe, life-threatening, or fatal) infections occurred in 30% of patients including unspecified pathogen, bacterial, fungal and viral infections in 23%, 8%, 2% and 4% of patients respectively.

8.2.1 Monitoring and management guidance

Severe infections, which could be life threatening, were very commonly observed with Tecartus. Patients must be monitored for signs and symptoms of infection before, during and after infusion and treated appropriately. Prophylactic antibiotics must be administered according to standard institutional guidelines. Febrile neutropenia has been observed in patients after Tecartus infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated. In immunosuppressed patients, life threatening and fatal opportunistic infections including disseminated fungal infections and viral reactivation (e.g., HHV 6 and progressive multifocal leukoencephalopathy) have been reported. The possibility of these infections should be considered in patients with neurologic events and appropriate diagnostic evaluations should be performed.

9. PROLONGED CYTOPENIAS

9.1 Yescarta

Grade 3 or higher neutropenia (including febrile neutropenia), anemia, and thrombocytopenia occurred in 68%, 31%, and 23% of patients, respectively. Prolonged (still present at Day 30 or with an onset at Day 30 or beyond) Grade 3 or higher neutropenia, thrombocytopenia, and anemia occurred in 26%, 12%, and 6% of patients, respectively. In ZUMA-1, at the time of the 24-month follow-up analysis, Grade 3 or higher neutropenia, thrombocytopenia, and anemia present after Day 93 occurred in 11%, 7%, and 3% of patients, respectively. In ZUMA-7, Grade 3 or higher neutropenia and thrombocytopenia were reported in 94% and 26% of patients treated with Yescarta.

9.2 Tecartus

Cytopenias are very common following prior lymphodepleting chemotherapy and Tecartus therapy. Prolonged (present on or beyond Day 30 or with an onset at Day 30 or beyond) Grade 3 or higher cytopenias occurred in 48% of patients and included neutropenia (34%), thrombocytopenia (27%), and anemia (15%).

9.3 Management guidance for Yescarta and Tecartus

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and Yescarta or Tecartus infusion and must be managed according to standard guidelines. Grade 3 or higher prolonged cytopenias following Yescarta or Tecartus infusion occurred very commonly and included thrombocytopenia, neutropenia, and anemia. Patient blood counts must be monitored after Yescarta or Tecartus infusion.

10. HYPOGAMMAGLOBULINAEMIA

10.1 Yescarta

Hypogammaglobulinemia was reported in 15% of patients treated with Yescarta. Cumulatively, 36 (33%) of 108 patients in ZUMA-1 received intravenous immunoglobulin therapy by the time of the 54-month analysis, 28 (16%) of 170 patients in ZUMA-7 received intravenous immunoglobulin therapy by the time of the 23.2 Month analysis and 33 (28%) of 119 subjects in ZUMA-5 received intravenous immunoglobulin therapy at the time of the 24-month follow-up analysis. In ZUMA-7, immunoglobulins decreased was reported in 11% of patients treated with Yescarta.

10.2 Tecartus

Hypogammaglobulinemia occurred in 12% of patients. Grade 3 or higher hypogammaglobulinemia occurred in 1% of patients.

10.3 Management guidance for Yescarta and Tecartus

B cell aplasia leading to hypogammaglobulinemia can occur in patients receiving treatment with Yescarta or Tecartus. Immunoglobulin levels should be monitored after treatment with Yescarta or Tecartus and managed using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement.

II. POST YESCARTA OR TECARTUS INFUSION MONITORING

Post Yescarta or Tecartus infusion recommendations:

- Patients should 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 hospitalization for the first 10 days post infusion or at the first signs or symptoms of CRS and/or neurologic adverse reaction.
- Patients stay within proximity (no more than 2 hours away) of the qualified clinical facility 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 reaction, they should be instructed to immediately go to the qualified clinical facility (or nearest hospital if travel is deemed unsafe) for evaluation for hospitalization 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 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 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 or Tecartus infusion?		

12. 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 minimize 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 diarrhea
- Fast or irregular heartbeat
- Severe fatigue or weakness

Provide the Yescarta or 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 (no more than 2 hours away) of a qualified clinical facility for a minimum of 4 weeks to monitor for signs and symptoms of CRS or neurologic adverse reactions.

13. REPORTING OF ADVERSE REACTIONS

Reporting suspected adverse reactions after authorization 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 Authorization Holder Gilead Sciences Israel Ltd or the Ministry of Health.

Please contact the Ministry of Health using the link **https://sideeffects.health.gov.il** or through the registration holder: **Safety_FC@gilead.com.**

14. REFERENCES

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