YESCARTA- axicabtagene ciloleucel suspension
Kite Pharma, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use YESCARTA safely and effectively. See full prescribing information for YESCARTA.
YESCARTA™ (axicabtagene ciloleucel) suspension for intravenous infusion
Initial U.S. Approval: October 2017

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGIC TOXICITIES
See full prescribing information for complete boxed warning.

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving YESCARTA. Do not administer YESCARTA to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids (2.2, 2.3, 5.1).**
- **Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving YESCARTA, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with YESCARTA. Provide supportive care and/or corticosteroids, as needed (2.2, 2.3, 5.2).**
- **YESCARTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA REMS (5.3).**

INDICATIONS AND USAGE

YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Limitation of Use: YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma (1).

DOSAGE AND ADMINISTRATION

For autologous use only. For intravenous use only.

- Do NOT use a leukodepleting filter.
- Administer a lymphodepleting regimen of cyclophosphamide and fludarabine before infusion of YESCARTA (2.2).
- Verify the patient's identity prior to infusion (2.2).
- Premedicate with acetaminophen and an H1-antihistamine (2.2).
- Confirm availability of tocilizumab prior to infusion (2.1, 5.1).
- Dosing of YESCARTA is based on the number of chimeric antigen receptor (CAR)-positive viable T cells (2.1).
- The target YESCARTA dose is 2×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 CAR-positive viable T cells (2.1).
- Administer YESCARTA in a certified healthcare facility (2.2, 5.1, 5.2, 5.3).

DOSAGE FORMS AND STRENGTHS

- YESCARTA is available as a cell suspension for infusion.
- YESCARTA comprises a suspension of 2×10^6 CAR-positive viable T cells per kg of body weight, with a maximum of 2×10^8 CAR-positive viable T cells in approximately 68 mL (3).

CONTRAINDICATIONS

• None (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Monitor for hypersensitivity reactions during infusion (5.4).
- Serious Infections: Monitor patients for signs and symptoms of infection; treat appropriately (5.5).
- Prolonged Cytopenias: Patients may exhibit Grade 3 or higher cytopenias for several weeks following YESCARTA

infusion. Monitor complete blood counts (5.6).
- Hypogammaglobulinemia: Monitor and provide replacement therapy (5.7).
- Secondary Malignancies: In the event that a secondary malignancy occurs after treatment with YESCARTA, contact Kite at 1-844-454-KITE (5483) (5.8).
- Effects on Ability to Drive and Use Machines: Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks after receiving YESCARTA (5.9).

WARNINGS AND PRECAUTIONS

ADVERSE REACTIONS

The most common non-laboratory adverse reactions (incidence greater than or equal to 20%) are: cytokine release syndrome, fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections-pathogen unspecified, nausea, hypoxia, tremor, cough, vomiting, dizziness, constipation, and cardiac arrhythmias. (5.4, 6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Kite at 1-844-454-KITE (5483) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITIES

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving YESCARTA. Do not administer YESCARTA to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids *[see Dosage and Administration (2.2, 2.3), Warnings and Precautions (5.1)].***
- **Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving YESCARTA, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with YESCARTA. Provide supportive care and/or corticosteroids as needed *[see Dosage and Administration (2.2, 2.3), Warnings and Precautions (5.2)].***
- **YESCARTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA REMS *[see Warnings and Precautions (5.3)].***

1 INDICATIONS AND USAGE

YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Limitation of Use: YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.

2 DOSAGE AND ADMINISTRATION

For autologous use only. For intravenous use only.

2.1 Dose

Each single infusion bag of YESCARTA contains a suspension of chimeric antigen receptor (CAR)-positive T cells in approximately 68 mL. The target dose is 2×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 CAR-positive viable T cells.

2.2 Administration

YESCARTA is for autologous use only. The patient's identity must match the patient identifiers on the YESCARTA cassette and infusion bag. Do not infuse YESCARTA if the information on the patient-specific label does not match the intended patient *[see Dosage and Administration (2.2.3)]*.

Preparing Patient for YESCARTA Infusion

Confirm availability of YESCARTA prior to starting the lymphodepleting regimen.

Pre-treatment

- Administer a lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m2 intravenously and fludarabine 30 mg/m2 intravenously on the fifth, fourth, and third day before infusion of YESCARTA.

Premedication

- Administer acetaminophen 650 mg PO and diphenhydramine 12.5 mg intravenously or PO approximately 1 hour before YESCARTA infusion.
- Avoid prophylactic use of systemic corticosteroids, as it may interfere with the activity of YESCARTA.

Preparation of YESCARTA for Infusion

Coordinate the timing of YESCARTA thaw and infusion. Confirm the infusion time in advance, and adjust the start time of YESCARTA thaw such that it will be available for infusion when the patient is ready.

- Confirm patient identity: Prior to YESCARTA preparation, match the patient's identity with the patient identifiers on the YESCARTA cassette.
- Do not remove the YESCARTA product bag from the cassette if the information on the patient-specific label does not match the intended patient.
- Once patient identification is confirmed, remove the YESCARTA product bag from the cassette and check that the patient information on the cassette label matches the bag label.
- Inspect the product bag for any breaches of container integrity such as breaks or cracks before thawing. If the bag is compromised, follow the local guidelines (or call Kite at 1-844-454-KITE).
- Place the infusion bag inside a second sterile bag per local guidelines.
- Thaw YESCARTA at approximately 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Do not wash, spin down, and/or re-suspend YESCARTA in new media prior to infusion.
- Once thawed, YESCARTA may be stored at room temperature (20°C to 25°C) for up to 3 hours.

Administration

- For autologous use only.
- Ensure that tocilizumab and emergency equipment are available prior to infusion and during the recovery period.
- Do NOT use a leukodepleting filter.
- Central venous access is recommended for the infusion of YESCARTA.
- Confirm the patient's identity matches the patient identifiers on the YESCARTA product bag.
- Prime the tubing with normal saline prior to infusion.
- Infuse the entire contents of the YESCARTA bag within 30 minutes by either gravity or a peristaltic pump. YESCARTA is stable at room temperature for up to 3 hours after thaw.
- Gently agitate the product bag during YESCARTA infusion to prevent cell clumping.
- After the entire content of the product bag is infused, rinse the tubing with normal saline at the same infusion rate to ensure all product is delivered.

YESCARTA contains human blood cells that are genetically modified with replication incompetent retroviral vector. Follow universal precautions and local biosafety guidelines for handling and disposal to avoid potential transmission of infectious diseases.

Monitoring

- Administer YESCARTA at a certified healthcare facility.
- Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS and neurologic toxicities.
- Instruct patients to remain within proximity of the certified healthcare facility for at least 4 weeks following infusion.

2.3 Management of Severe Adverse Reactions

Cytokine Release Syndrome

Identify CRS based on clinical presentation *[see Warnings and Precautions (5.1)]*. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 1. 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.

Table 1. CRS Grading and Management Guidance

CRS Grade *(a)*	**Tocilizumab**	**Corticosteroids**
Grade 1 Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	N/A	N/A
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO_2 or hypotension responsive to fluids or low-dose of one vasopressor or Grade 2 organ toxicity *(b)*.	Administer tocilizumab *(c)* 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab.
Grade 3 Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% FiO_2 or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis.	Per Grade 2	Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours). Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days.
Grade 4 Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD) or Grade 4 organ toxicity	Per Grade 2	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.

(excluding transaminitis).

(a) Lee et al 2014

(b) Refer to Table 2 for management of neurologic toxicity

(c) Refer to tocilizumab Prescribing Information for details

Neurologic Toxicity

Monitor patients for signs and symptoms of neurologic toxicities (Table 2). Rule out other causes of neurologic symptoms. 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. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis for any Grade 2 or higher neurologic toxicities.

Table 2. Neurologic Toxicity Grading and Management Guidance

Grading Assessment	Concurrent CRS	No Concurrent CRS
Grade 2	Administer tocilizumab per Table 1 for management of Grade 2 CRS. If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
Grade 3	Administer tocilizumab per Table 1 for management of Grade 2 CRS. In addition, administer dexamethasone 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
Grade 4	Administer tocilizumab per Table 1 for management of Grade 2 CRS. Administer methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 more days; if improves, then manage as above. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.

3 DOSAGE FORMS AND STRENGTHS

YESCARTA is available as a cell suspension for infusion.

A single dose of YESCARTA contains 2×10^6 CAR-positive viable T cells per kg of body weight (or maximum of 2×10^8 CAR-positive viable T cells for patients 100 kg and above) in approximately 68 mL suspension in an infusion bag *[see How Supplied/Storage and Handling (16)]*.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome (CRS)

CRS, including fatal or life-threatening reactions, occurred following treatment with YESCARTA. In Study 1, CRS occurred in 94% (101/108) of patients receiving YESCARTA, including ≥ Grade 3 (Lee grading system[1]) CRS in 13% (14/108) of patients. Among patients who died after receiving YESCARTA, four had ongoing CRS events at the time of death. The median time to onset was 2 days (range: 1 to 12 days) and the median duration of CRS was 7 days (range: 2 to 58 days). Key manifestations of CRS include fever (78%), hypotension (41%), tachycardia (28%), hypoxia (22%), and chills (20%). 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) *[see Adverse Reactions (6)]*.

Ensure that 2 doses of tocilizumab are available prior to infusion of YESCARTA. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for 4 weeks after infusion. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time *[see Patient Counseling Information (17)]*. At the first sign of CRS, institute treatment with supportive care, tocilizumab or tocilizumab and corticosteroids as indicated *[see Dosage and Administration (2.3)]*.

5.2 Neurologic Toxicities

Neurologic toxicities, that were fatal or life-threatening, occurred following treatment with YESCARTA. Neurologic toxicities occurred in 87% of patients. Ninety-eight percent of all neurologic toxicities occurred within the first 8 weeks of YESCARTA infusion, with a median time to onset of 4 days (range: 1 to 43 days). The median duration of neurologic toxicities was 17 days. Grade 3 or higher neurologic toxicities occurred in 31% of patients.

The most common neurologic toxicities included encephalopathy (57%), headache (44%), tremor (31%), dizziness (21%), aphasia (18%), delirium (17%), insomnia (9%) and anxiety (9%). Prolonged encephalopathy lasting up to 173 days was noted. Serious events including leukoencephalopathy and seizures occurred with YESCARTA. Fatal and serious cases of cerebral edema have occurred in patients treated with YESCARTA.

Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of neurologic toxicities. Monitor patients for signs or symptoms of neurologic toxicities for 4 weeks after infusion and treat promptly *[see Management of Severe Adverse Reactions (2.3); Neurologic Toxicities]*.

5.3 YESCARTA REMS

Because of the risk of CRS and neurologic toxicities, YESCARTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA REMS *[see Boxed Warning and Warnings and Precautions (5.1 and 5.2)]*. The required components of the YESCARTA REMS are:

- Healthcare facilities that dispense and administer YESCARTA must be enrolled and comply with the

REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of two doses of tocilizumab are available for each patient for infusion within 2 hours after YESCARTA infusion, if needed for treatment of CRS.
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer YESCARTA are trained about the management of CRS and neurologic toxicities.

Further information is available at www.YescartaREMS.com or 1-844-454-KITE (5483).

5.4 Hypersensitivity Reactions

Allergic reactions may occur with the infusion of YESCARTA. Serious hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide (DMSO) or residual gentamicin in YESCARTA.

5.5 Serious Infections

Severe or life-threatening infections occurred in patients after YESCARTA infusion. In Study 1, infections (all grades) occurred in 38% of patients. Grade 3 or higher infections occurred in 23% of patients. Grade 3 or higher infections with an unspecified pathogen occurred in 16% of patients, bacterial infections in 9%, and viral infections in 4%. YESCARTA should not be administered to patients with clinically significant active systemic infections. Monitor patients for signs and symptoms of infection before and after YESCARTA infusion and treat appropriately. Administer prophylactic anti-microbials according to local guidelines.

Febrile neutropenia was observed in 36% of 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.

Viral Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs directed against B cells. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing.

5.6 Prolonged Cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and YESCARTA infusion. In Study 1, Grade 3 or higher cytopenias not resolved by Day 30 following YESCARTA infusion occurred in 28% of patients and included thrombocytopenia (18%), neutropenia (15%), and anemia (3%). Monitor blood counts after YESCARTA infusion.

5.7 Hypogammaglobulinemia

B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with YESCARTA. In Study 1, hypogammaglobulinemia occurred in 15% of patients. Monitor immunoglobulin levels after treatment with YESCARTA and manage using infection precautions, antibiotic prophylaxis and immunoglobulin replacement.

The safety of immunization with live viral vaccines during or following YESCARTA treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during YESCARTA treatment, and until immune recovery following treatment with YESCARTA.

5.8 Secondary Malignancies

Patients treated with YESCARTA may develop secondary malignancies. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Kite at 1-844-454-KITE (5483) to obtain instructions on patient samples to collect for testing.

5.9 Effects on Ability to Drive and Use Machines

Due to the potential for neurologic events, including altered mental status or seizures, patients receiving YESCARTA are at risk for altered or decreased consciousness or coordination in the 8 weeks following YESCARTA infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Cytokine Release Syndrome *[see Warnings and Precautions (5.1, 5.3)]*
- Neurologic Toxicities *[see Warnings and Precautions (5.2, 5.3)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.4)]*
- Serious Infections *[see Warnings and Precautions (5.5)]*
- Prolonged Cytopenias *[see Warnings and Precautions (5.6)]*
- Hypogammaglobulinemia *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described in this section reflect exposure to YESCARTA in the clinical trial (Study 1) in which 108 patients with relapsed/refractory B-cell NHL received CAR-positive T cells based on a recommended dose which was weight-based *[see Clinical Trials (14)]*. Patients with a history of CNS disorders (such as seizures or cerebrovascular ischemia) or autoimmune disease requiring systemic immunosuppression were ineligible. The median duration of follow up was 8.7 months. The median age of the study population was 58 years (range: 23 to 76 years); 68% were men. The baseline ECOG performance status was 43% with ECOG 0, and 57% with ECOG 1.

The most common adverse reactions (incidence ≥ 20%) include CRS, fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections-pathogen unspecified, nausea, hypoxia, tremor, cough, vomiting, dizziness, constipation, and cardiac arrhythmias. Serious adverse reactions occurred in 52% of patients. The most common serious adverse reactions (> 2%) include encephalopathy, fever, lung infection, febrile neutropenia, cardiac arrhythmia, cardiac failure, urinary tract infection, renal insufficiency, aphasia, cardiac arrest, *Clostridium difficile* infection, delirium, hypotension, and hypoxia.

The most common (≥ 10%) Grade 3 or higher reactions include febrile neutropenia, fever, CRS, encephalopathy, infections-pathogen unspecified, hypotension, hypoxia, and lung infections.

Forty-five percent (49/108) of patients received tocilizumab after infusion of YESCARTA.

Table 3 summarizes the adverse reactions that occurred in at least 10% of patients treated with YESCARTA and Table 4 describes the laboratory abnormalities of Grade 3 or 4 that occurred in at least 10% of patients.

Table 3. Summary of Adverse Reactions Observed in at Least 10% of the Patients Treated with YESCARTA in Study 1

Adverse Reaction	Any Grade (%)	Grade 3 or Higher (%)
Cardiac Disorders		
Tachycardia[a]	57	2
Arrhythmia[b]	23	7
Gastrointestinal Disorders		

Diarrhea	38	4
Nausea	34	0
Vomiting	26	1
Constipation	23	0
Abdominal pain[c]	14	1
Dry mouth	11	0
General Disorders and Administration Site Conditions		
Fever	86	16
Fatigue[d]	46	3
Chills	40	0
Edema[e]	19	1
Immune System Disorders		
Cytokine release syndrome	94	13
Hypogammaglobulinemia[f]	15	0
Infections and Infestations		
Infections-pathogen unspecified	26	16
Viral infections	16	4
Bacterial infections	13	9
Investigations		
Decreased appetite	44	2
Weight decreased	16	0
Dehydration	11	3
Musculoskelatal and Connective Tissue Disorders		
Motor dysfunction[g]	19	1
Pain in extremity[h]	17	2
Back pain	15	1
Muscle pain	14	1
Arthralgia	10	0
Nervous System Disorders		
Encephalopathy[i]	57	29
Headache[j]	45	1
Tremor	31	2
Dizziness[k]	21	1
Aphasia[l]	18	6
Psychiatric Disorders		
Delirium[m]	17	6
Respiratory, Thoracic and Mediastinal Disorders		
Hypoxia[n]	32	11
Cough[o]	30	0
Dyspnea[p]	19	3
Pleural effusion	13	2
Renal and Urinary Disorders		
Renal insufficiency	12	5
Vascular Disorders		
Hypotension[q]	57	15
Hypertension	15	6
Thrombosis[r]	10	1

The following events were also counted in the incidence of CRS: tachycardia, arrhythmia, fever, chills, hypoxia, renal insufficiency, and hypotension.

[a]*Tachycardia includes tachycardia, sinus tachycardia.*

[b]*Arrhythmia includes arrhythmia, atrial fibrillation, atrial flutter, atrioventricular block, bundle branch block right, electrocardiogram QT prolonged, extra-systoles, heart rate irregular, supraventricular extra systoles, supraventricular tachycardia, ventricular arrhythmia, ventricular tachycardia.*

[c]*Abdominal pain includes abdominal pain, abdominal pain lower, abdominal pain upper.*
[d]*Fatigue includes fatigue, malaise.*
[e]*Edema includes face edema, generalized edema, local swelling, localized edema, edema, edema genital, edema peripheral, periorbital edema, peripheral swelling, scrotal edema.*
[f]*Hypogammaglobulinemia includes hypogammaglobulinemia, blood immunoglobulin D decreased, blood immunoglobulin G decreased.*
[g]*Motor dysfunction includes muscle spasms, muscular weakness.*
[h]*Pain in extremity includes pain not otherwise specified, pain in extremity.*
[i]*Encephalopathy includes cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, encephalopathy, hypersomnia, leukoencephalopathy, memory impairment, mental status changes, paranoia, somnolence, stupor.*
[j]*Headache includes headache, head discomfort, sinus headache, procedural headache.*
[k]*Dizziness includes dizziness, presyncope, syncope.*
[l]*Aphasia includes aphasia, dysphasia.*
[m]*Delirium includes agitation, delirium, delusion, disorientation, hallucination, hyperactivity, irritability, restlessness.*
[n]*Hypoxia includes hypoxia, oxygen saturation decreased.*
[o]*Cough includes cough, productive cough, upper-airway cough syndrome.*
[p]*Dyspnea includes acute respiratory failure, dyspnea, orthopnea, respiratory distress.*
[q]*Hypotension includes diastolic hypotension, hypotension, orthostatic hypotension.*
[r]*Thrombosis includes deep vein thrombosis, embolism, embolism venous, pulmonary embolism, splenic infarction, splenic vein thrombosis, subclavian vein thrombosis, thrombosis, thrombosis in device.*

Other clinically important adverse reactions that occurred in less than 10% of patients treated with YESCARTA include the following:

- *Blood and lymphatic system disorders:* Coagulopathy (2%)
- *Cardiac disorders:* Cardiac failure (6%) and cardiac arrest (4%)
- *Immune system disorders*: Hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) (1%), hypersensitivity (1%)
- *Infections and infestations disorders:* Fungal infections (5%)
- *Nervous system disorders:* Ataxia (6%), seizure (4%), dyscalculia (2%), and myoclonus (2%)
- *Respiratory, thoracic and mediastinal disorders:* Pulmonary edema (9%)
- *Skin and subcutaneous tissue disorders:* Rash (9%)
- *Vascular disorders:* Capillary leak syndrome (3%)

Laboratory Abnormalities:

Table 4. Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Patients in Study 1 Following Treatment with YESCARTA based on CTCAE (N=108)

	Grades 3 or 4 (%)
Lymphopenia	100
Leukopenia	96
Neutropenia	93
Anemia	66
Thrombocytopenia	58
Hypophosphatemia	50
Hyponatremia	19
Uric acid increased	13
Direct Bilirubin increased	13
Hypokalemia	10
Alanine Aminotransferase increased	10

6.2 Immunogenicity

YESCARTA has the potential to induce anti-product antibodies. The immunogenicity of YESCARTA has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR. Three patients tested positive for pre-dose anti-FMC63 antibodies at baseline and Months 1, 3, or 6 in Study 1. There is no evidence that the kinetics of initial expansion and persistence of YESCARTA, or the safety or effectiveness of YESCARTA, was altered in these patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with YESCARTA use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with YESCARTA to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if YESCARTA has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia. Therefore, YESCARTA is not recommended for women who are pregnant, and pregnancy after YESCARTA infusion should be discussed with the treating physician.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of YESCARTA in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for YESCARTA and any potential adverse effects on the breastfed infant from YESCARTA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy status of females with reproductive potential should be verified. Sexually-active females of reproductive potential should have a pregnancy test prior to starting treatment with YESCARTA.

Contraception

See the prescribing information for fludarabine and cyclophosphamide for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with YESCARTA.

Infertility

There are no data on the effect of YESCARTA on fertility.

8.4 Pediatric Use

The safety and efficacy of YESCARTA have not been established in pediatric patients.

8.5 Geriatric Use

Clinical trials of YESCARTA did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently or have different safety outcomes as compared to younger patients.

11 DESCRIPTION

YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy. To prepare YESCARTA, a patient's own T cells are harvested and genetically modified ex vivo by retroviral transduction to express a chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment (scFv) linked to CD28 and CD3-zeta co-stimulatory domains. The anti-CD19 CAR T cells are expanded and infused back into the patient, where they can recognize and eliminate CD19-expressing target cells.

YESCARTA is prepared from the patient's peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure. The mononuclear cells are enriched for T cells and activated with anti-CD3 antibody in the presence of IL-2, then transduced with the replication incompetent retroviral vector containing the anti-CD19 CAR transgene. The transduced T cells are expanded in cell culture, washed, formulated into a suspension, and cryopreserved. The product must pass a sterility test before release for shipping as a frozen suspension in a patient-specific infusion bag. The product is thawed prior to infusion *[see Dosage and Administration (2.2), How Supplied/Storage and Handling (16)]*.

In addition to T cells, YESCARTA may contain NK and NK-T cells. The formulation contains 5% dimethylsulfoxide (DMSO) and 2.5% albumin (human).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

YESCARTA, a CD19-directed genetically modified autologous T cell immunotherapy, binds to CD19-expressing cancer cells and normal B cells. Studies demonstrated that following anti-CD19 CAR T cell engagement with CD19-expressing target cells, the CD28 and CD3-zeta co-stimulatory domains 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 cells.

12.2 Pharmacodynamics

After YESCARTA infusion, pharmacodynamic responses were evaluated over a 4-week interval by measuring transient elevation of cytokines, chemokines and other molecules in blood. Levels of cytokines and chemokines such as IL-6, IL-8, IL-10, IL-15, TNF-α, IFN-γ, and sIL2Rα were analyzed. Peak elevation was observed within the first 14 days after infusion, and levels generally returned to baseline within 28 days.

Due to the on-target effect of YESCARTA, a period of B-cell aplasia is expected.

12.3 Pharmacokinetics

Following infusion of YESCARTA, anti-CD19 CAR T cells exhibited an initial rapid expansion followed by a decline to near baseline levels by 3 months. Peak levels of anti-CD19 CAR T cells occurred within the first 7-14 days after YESCARTA infusion.

Age (range: 23 – 76 years) and gender had no significant impact on AUC Day 0 - 28 and Cmax of YESCARTA.

The number of anti-CD19 CAR T cells in blood was positively associated with objective response [complete remission (CR) or partial remission (PR)]. The median anti-CD19 CAR T cell Cmax levels in responders (n=73) were 205% higher compared to the corresponding level in nonresponders (n=23)

(43.6 cells/μL vs 21.2 cells/μL). Median AUC Day 0 - 28 in responding patients (n=73) was 251% of the corresponding level in nonresponders (n=23) (557.1 days × cells/μL vs. 222.0 days × cells/μL).

Some patients required tocilizumab and corticosteroids for management of CRS and neurologic toxicities. Patients treated with tocilizumab (n=44) had 262% and 232% higher anti-CD19 CAR T cells as measured by AUC Day 0 - 28 and Cmax respectively, as compared to patients who did not receive tocilizumab (n=57). Similarly, patients that received corticosteroids (n=26) had 217% and 155% higher AUC Day 0 - 28 and C_{max} compared to patients who did not receive corticosteroids (n=75).

Hepatic and renal impairment studies of YESCARTA were not conducted.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with YESCARTA. No studies have been conducted to evaluate the effects of YESCARTA on fertility.

14 CLINICAL STUDIES

Relapsed or Refractory Large B-Cell Lymphoma

A single-arm, open-label, multicenter trial evaluated the efficacy of a single infusion of YESCARTA in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma. Eligible patients had refractory disease to the most recent therapy or relapse within 1 year after autologous hematopoietic stem cell transplantation (HSCT). The study excluded patients with prior allogeneic HSCT, any history of central nervous system lymphoma, ECOG performance status of 2 or greater, absolute lymphocyte count less than 100/μL, creatinine clearance less than 60 mL/min, hepatic transaminases more than 2.5 times the upper limit of normal, cardiac ejection fraction less than 50%, or active serious infection.

Following lymphodepleting chemotherapy, YESCARTA was administered as a single intravenous infusion at a target dose of 2×10^6 CAR-positive viable T cells/kg (maximum permitted dose: 2×10^8 cells). The lymphodepleting regimen consisted of cyclophosphamide 500 mg/m^2 intravenously and fludarabine 30 mg/m^2 intravenously, both given on the fifth, fourth, and third day before YESCARTA. Bridging chemotherapy between leukapheresis and lymphodepleting chemotherapy was not permitted. All patients were hospitalized for YESCARTA infusion and for a minimum of 7 days afterward.

Of 111 patients who underwent leukapheresis, 101 received YESCARTA. Of the patients treated, the median age was 58 years (range: 23 to 76), 67% were male, and 89% were white. Most (76%) had DLBCL, 16% had transformed follicular lymphoma, and 8% had primary mediastinal large B-cell lymphoma. The median number of prior therapies was 3 (range: 1 to 10), 77% of the patients had refractory disease to a second or greater line of therapy, and 21% had relapsed within 1 year of autologous HSCT.

One out of 111 patients did not receive the product due to manufacturing failure. Nine other patients were not treated, primarily due to progressive disease or serious adverse reactions following leukapheresis. The median time from leukapheresis to product delivery was 17 days (range: 14 to 51 days), and the median time from leukapheresis to infusion was 24 days (range: 16 to 73 days). The median dose was 2.0×10^6 CAR-positive viable T cells/kg (range: 1.1 to 2.2×10^6 cells/kg).

Efficacy was established on the basis of complete remission (CR) rate and duration of response (DOR), as determined by an independent review committee (Table 5 and Table 6). The median time to response was 0.9 months (range: 0.8 to 6.2 months). Response durations were longer in patients who achieved CR, as compared to patients with a best response of partial remission (PR) (Table 6). Of the 52 patients who achieved CR, 14 initially had stable disease (7 patients) or PR (7 patients), with a median time to improvement of 2.1 months (range: 1.6 to 5.3 months).

Table 5. Response Rate

	Recipients of YESCARTA (N = 101)
Objective Response Rate[a]	73 (72%)
(95% CI)	(62, 81)
Complete Remission Rate	52 (51%)
(95% CI)	(41, 62)
Partial Remission Rate	21 (21%)
(95% CI)	(13, 30)

CI, confidence interval.

[a]*Per 2007 revised International Working Group criteria, as assessed by the independent review committee.*

Table 6. Duration of Response

	From N of 101
Number of Responders	73
DOR (Months)[a]	
Median[b]	9.2
(95% CI)	(5.4, NE)
Range[c]	0.03+, 14.4+
DOR if Best Response is CR (Months)	
Median[b]	NE
(95% CI)	(8.1, NE)
Range[c]	0.4, 14.4+
DOR if Best Response is PR (Months)	
Median[b]	2.1
(95% CI)	(1.3, 5.3)
Range[c]	0.03+, 8.4+
Median Follow-up for DOR (Months)[a, b]	7.9

CR, complete remission; DOR, duration of response; NE, not estimable; PR, partial remission.

[a]*Among all responders. DOR is measured from the date of first objective response to the date of progression or death from relapse or toxicity.*

[b]*Kaplan-Meier estimate.*

[c]*A + sign indicates a censored value.*

15 REFERENCES

1. Lee DW et al (2014). Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014 Jul 10; 124(2): 188–195.

16 HOW SUPPLIED/STORAGE AND HANDLING

YESCARTA is supplied in an infusion bag (NDC 71287-119-01) containing approximately 68 mL of frozen suspension of genetically modified autologous T cells in 5% DMSO and 2.5% albumin (human).

Each YESCARTA infusion bag is individually packed in a metal cassette (NDC 71287-119-02). YESCARTA is stored in the vapor phase of liquid nitrogen and supplied in a liquid nitrogen dry shipper.

- Match the identity of the patient with the patient identifiers on the cassette and infusion bag upon receipt.
- Store YESCARTA frozen in the vapor phase of liquid nitrogen (less than or equal to minus 150°C).
- Thaw before using *[see Dosage and Administration (2)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Ensure that patients understand the risk of manufacturing failure (1% in clinical trial). In case of a manufacturing failure, a second manufacturing of YESCARTA may be attempted. In addition, while the patient awaits the product, additional chemotherapy (not the lymphodepletion) may be necessary and may increase the risk of adverse events during the pre-infusion period.

Advise patients to seek immediate attention for any of the following:
- Cytokine Release Syndrome (CRS) - Signs or symptoms associated with CRS including fever, chills, fatigue, tachycardia, nausea, hypoxia, and hypotension. *[see Warnings and Precautions (5.1) and Adverse Reactions (6)]*.
- Neurologic Toxicities – Signs or symptoms associated with neurologic events including encephalopathy, seizures, changes in level of consciousness, speech disorders, tremors, and confusion *[see Warnings and Precautions (5.2) and Adverse Reactions (6)]*.
- Serious Infections - Signs or symptoms associated with infection *[see Warnings and Precautions (5.3) and Adverse Reactions (6)]*.
- Prolonged Cytopenia - Signs or symptoms associated with bone marrow suppression including neutropenia, anemia, thrombocytopenia, or febrile neutropenia *[see Warnings and Precautions (5.5) and Adverse Reactions (6)]*.

Advise patients for the need to:
- Refrain from driving or operating heavy or potentially dangerous machinery after YESCARTA infusion until at least 8 weeks after infusion *[see Warnings and Precautions (5.2)]*.
- Have periodic monitoring of blood counts.
- Contact Kite at 1-844-454-KITE (5483) if they are diagnosed with a secondary malignancy *[see Warnings and Precautions (5.8)]*.

Manufactured by, Packed by, Distributed by:
Kite Pharma, Inc.
Santa Monica, CA 90404
US License No 2064

MEDICATION GUIDE
YESCARTA (pronounced yes-kar-ta)
(axicabtagene ciloleucel)

Read this Medication Guide before you start your YESCARTA treatment. The more you know about your treatment, the more active you can be in your care. Talk with your healthcare provider if you have questions about your health condition or treatment. Reading this Medication Guide does not take the place of talking with your healthcare provider about your treatment.

What is the most important information I should know about YESCARTA?

YESCARTA may cause side effects that are life-threatening and can lead to death. Call or see your healthcare provider or get emergency help right away if you get any of the following:
- Fever (100.4°F/38°C or higher)
- Difficulty breathing
- Chills or shaking chills

- Confusion
- Dizziness or lightheadedness
- Severe nausea, vomiting, or diarrhea
- Fast or irregular heartbeat
- Severe fatigue or weakness

It is important to tell your healthcare provider that you received YESCARTA and to show them your YESCARTA Patient Wallet Card. Your healthcare provider may give you other medicines to treat your side effects.

What is YESCARTA?

YESCARTA is a treatment for your non-Hodgkin lymphoma. It is used when you have failed at least two other kinds of treatment. YESCARTA is different than other cancer medicines because it is made from your own white blood cells, which have been modified to recognize and attack your lymphoma cells.

Before getting YESCARTA, tell your healthcare provider about all your medical problems, including if you have or have had:
- Neurologic problems (such as seizures, stroke, or memory loss)
- Lung or breathing problems
- Heart problems
- Liver problems
- Kidney problems
- A recent or active infection

Tell your healthcare provider about all the medications you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive YESCARTA?
- Since YESCARTA is made from your own white blood cells, your blood will be collected by a process called “leukapheresis” (loo-kah-fur-ee-sis), which will concentrate your white blood cells.
- Your blood cells will be sent to a manufacturing center to make your YESCARTA.
- Before you get YESCARTA, you will get 3 days of chemotherapy to prepare your body.
- When your YESCARTA is ready, your healthcare provider will give it to you through a catheter placed into your vein (intravenous infusion). The infusion usually takes less than 30 minutes.
- You will be monitored where you received your treatment daily for at least 7 days after the infusion.
- You should plan to stay close to the location where you received your treatment for at least 4 weeks after getting YESCARTA. Your healthcare provider will help you with any side effects that may occur.
- You may be hospitalized for side effects and your healthcare provider will discharge you if your side effects are under control, and it is safe for you to leave the hospital.
- Your healthcare provider will want to do blood tests to follow your progress. It is important that you do have your blood tested. If you miss an appointment, call your healthcare provider as soon as possible to reschedule.

What should I avoid after receiving YESCARTA?
- Do not drive, operate heavy machinery, or do other dangerous things for 8 weeks after you get YESCARTA because the treatment can cause sleepiness, confusion, weakness, temporary memory and coordination problems.
- Do not donate blood, organs, tissues, and cells for transplantation.

What are the possible or reasonably likely side effects of YESCARTA?

The most common side effects of YESCARTA include:
- Fever (100.4°F/38°C or higher)

- Low white blood cells (can occur with a fever)
- Low red blood cells
- Low blood pressure (dizziness or lightheadedness, headache, feeling tired, short of breath)
- Fast heartbeat
- Confusion
- Difficulty speaking or slurred speech
- Nausea
- Diarrhea

These are not all the possible side effects of YESCARTA. Call your healthcare provider about any side effects that concern you. You may report side effects to the FDA at 1-800-FDA-1088.

General information about the safe and effective use of YESCARTA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about YESCARTA, talk with your healthcare provider. You can ask your healthcare provider for information about YESCARTA that is written for health professionals. You can get additional information by contacting Kite at 1-844-454-KITE (5483) or at www.Yescarta.com.

What are the ingredients in YESCARTA?

Active ingredients: axicabtagene ciloleucel.

Inactive ingredients: albumin (human); DMSO.

Package/Label Principal Display Panel

axicabtagene ciloleucel

YESCARTA

NDC 71287-119-01

RX ONLY

FOR AUTOLOGOUS & INTRAVENOUS USE ONLY

No U.S. standard of potency

Dose: One Sterile bag for infusion

Contents: Maximum of 2 x 10^8 autologous anti-CD19 CAR T cells in approximately 68 mL suspension containing 5% DMSO USP

Gently mix the contents of the bag while thawing

See package insert for full prescribing information and instructions for administration ship and store in vapor phase of liquid nitrogen ≤ -150°C

DO NOT FILTER

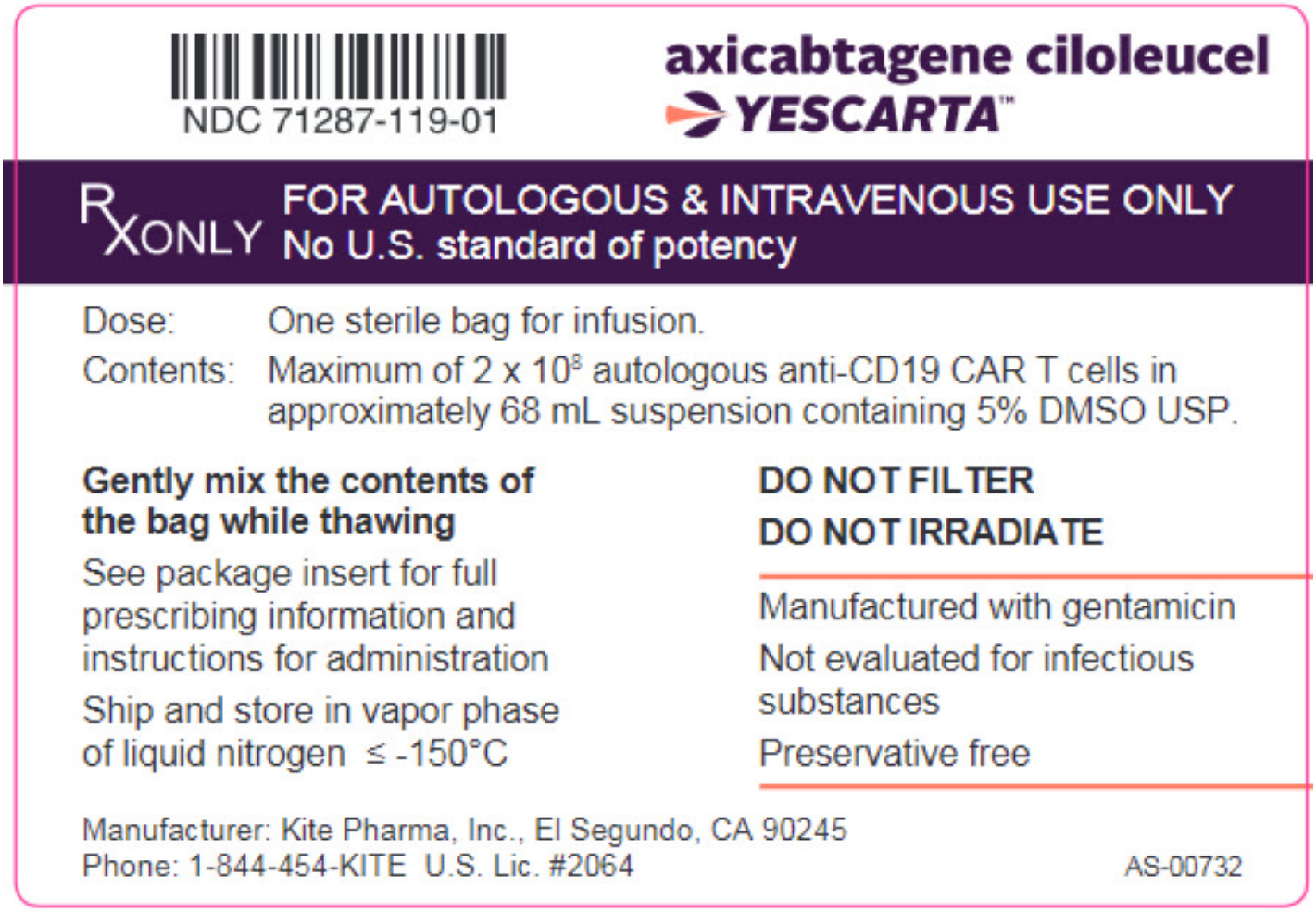
DO NOT IRRADIATE

Manufactured with gentamicin

Not evaluated for infectious substances

Preservative free

Manufacturer: Kite Pharma, Inc., El Segundo, CA 90245
Phone: 1-844-454-KITE U.S. Lic. #2064
AS-00732



Package/Label Principal Display Panel

VERIFY PATIENT ID

axicabtagene ciloleucel

YESCARTA

Lot: 123456789-0X

Kite Patient ID: 123456789

Expiration Date: 31-Dec-2900

First Name M.I.: FIRST NAME W

Last Name: LAST NAME

D.O.B.: 31-Dec-1900

Hospital Patient ID: 1234567890123456

D.I.N:

AS-00731 W0123 45 678900

Package/Label Principal Display Panel

axicabtagene ciloleucel

YESCARTA

STOP

Confirm patient ID prior to infusion

VERIFY PATIENT ID

Lot: 123456789-0X

Kite Patient ID: 123456789

Expiration Date: 31-Dec-2900

First Name M.I.: FIRST NAME W

Last Name: LAST NAME

D.O.B.: 31-Dec-1900

Hospital Patient ID: 1234567890123456

D.I.N:

AS-00731 W0123 45 678900

Package/Label Principal Display Panel

axicabtagene ciloleucel

YESCARTA

Kite Pharma, Inc.

Site: FXX

Cell Order: 1234567

LOT: 123456789-01

Mfg Address Street, City, State Postal Code
(XXX) XXX-XXXX

AS-00730

YESCARTA

axicabtagene ciloleucel suspension

Product Information			
Product Type	CELLULAR THERAPY	**Item Code (Source)**	NDC:71287-119
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
AXICABTAGENE CILOLEUCEL (UNII: U2I8T43Y7R) (AXICABTAGENE CILOLEUCEL - UNII:U2I8T43Y7R)	AXICABTAGENE CILOLEUCEL	2000000 in 68 mL

Inactive Ingredients	
Ingredient Name	**Strength**
DIMETHYL SULFOXIDE (UNII: YOW8V9698H)	
ALBUMIN HUMAN (UNII: ZIF514RVZR)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:71287-119-02	1 in 1 PACKAGE		
1	NDC:71287-119-01	68 mL in 1 BAG; Type 1: Convenience Kit of Co-Package		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125643	10/18/2017	

Labeler - Kite Pharma, Inc. (963353359)

Establishment

Name	Address	ID/FEI	Business Operations
Kite Pharma, Inc.		963353359	manufacture(71287-119) , label(71287-119)

Revised: 10/2017 Kite Pharma, Inc.