PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PRYESCARTA®

Axicabtagene ciloleucel

Cell suspension in patient-specific single infusion bag, target of 2 × 10^6 chimeric antigen receptor (CAR)-positive viable T cells per kg body weight with a maximum of 2 × 10^8 CAR-positive viable T cells, for intravenous infusion

Professed Standard

Other antineoplastic agent (Anatomical Therapeutic Chemical index code: L01X)

Kite Pharma Inc.
Santa Monica, CA 90404

Manufactured for:
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RECENT MAJOR LABEL CHANGES

Warnings and Precautions, Immune (8)	12/2020
Warnings and Precautions, Neurologic (8)	02/2020

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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 (LBCL) after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma (PMBCL), high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

1.1 Pediatrics (< 18 years of age)

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics (≥ 65 years of age)

Evidence from clinical studies is not sufficient to determine if the use of YESCARTA in patients ≥ 65 years of age is associated with differences in safety and effectiveness.

2 CONTRAINDICATIONS

YESCARTA is contraindicated in patients who are hypersensitive to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Cytokine Release Syndrome (CRS),** including fatal or life-threatening reactions, occurred in patients receiving YESCARTA. Delay YESCARTA treatment if a patient has active uncontrolled infection or inflammatory disorders, active graft-versus-host disease (GVHD) or unresolved serious adverse reactions from prior therapies. Monitor for CRS after treatment with YESCARTA. Provide supportive care, tocilizumab, or tocilizumab and corticosteroids, as needed (see **WARNINGS AND PRECAUTIONS**).
- **Neurologic adverse reactions**, including fatal or life-threatening reactions, occurred in patients receiving YESCARTA, including concurrently with CRS or independently of CRS. Monitor for neurologic adverse reactions after treatment with YESCARTA. Provide supportive care, tocilizumab (if with concurrent CRS), or corticosteroids, as needed (see **WARNINGS AND PRECAUTIONS**).
- YESCARTA should be administered by experienced health professionals at specialized treatment centres (see **WARNINGS AND PRECAUTIONS**).

4 DOSAGE AND ADMINISTRATION

YESCARTA should be administered by experienced health professionals at specialized treatment centers (see **WARNINGS AND PRECAUTIONS**).

4.1 Dosing Considerations

- For autologous use only; do NOT infuse YESCARTA if the information on the patient-specific label on the infusion bag does not match the intended patient.
- For intravenous (IV) use only; do NOT use a leukodepleting filter.
- Single infusion product
- Do NOT irradiate YESCARTA.
- Consider delaying lymphodepleting chemotherapy and YESCARTA treatment if the patient has one or more of the following conditions: clinically significant cardiac dysfunction, pulmonary dysfunction, renal insufficiency, acute neurologic toxicity, active uncontrolled infection or inflammation, and active graft-versus host disease (see **CLINICAL TRIALS**).

4.2 Recommended Dose and Dosage Adjustment

Adults

YESCARTA is provided as a single-dose, one-time treatment in a patient-specific infusion bag.

Each single infusion bag of YESCARTA contains a suspension of anti-CD19 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 (range: $1 \times 10^6 – 2.4 \times 10^6$ cells/kg), with a maximum of 2×10^8 CAR-positive viable T cells for patients 100 kg and above.

Pediatrics (< 18 years of age)

Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥ 65 years of age)

No dose adjustments are required for patients 65 years of age or older.

4.3 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.

Ensure that 4 doses of tocilizumab and access to emergency equipment are available prior to infusion and during the recovery period (see **WARNINGS AND PRECAUTIONS**).

Preparing Patient for YESCARTA Infusion

Confirm availability of YESCARTA prior to starting the lymphodepleting regimen.

Pre-treatment *(lymphodepleting chemotherapy)*

- Administer a lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m^2 IV and fludarabine 30 mg/m^2 intravenously on the 5th, 4th, and 3rd day before infusion of YESCARTA.

Premedication

- Administer acetaminophen 650 mg orally and diphenhydramine 12.5 to 25 mg intravenously or 25 mg orally 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 Konnect at 1-833-236-5483).
- Place the infusion bag inside a second sterile bag or 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 medium prior to infusion. Thawing should take approximately 3-5 minutes.
- Once thawed, YESCARTA may be stored at room temperature (20°C to 25°C) for up to 3 hours. Do NOT refreeze.

Administration

- For autologous use only.
- Ensure that 4 doses of tocilizumab and access to 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 0.9% sodium chloride solution prior to infusion.
- Infuse the entire content of the YESCARTA bag within 30 minutes by either gravity or a peristaltic pump. YESCARTA is stable at room temperature (20°C to 25°C) for up to 3 hours after thaw. Do NOT refreeze.
- 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 0.9% sodium chloride solution at the same infusion rate to ensure all YESCARTA is delivered.

4.4 Reconstitution

Not applicable.

4.5 Missed Dose

Not Applicable.

5 OVERDOSAGE

No data are available regarding overdosage.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous Infusion	Each patient-specific, single infusion bag of YESCARTA contains a suspension of anti-CD19 CAR-positive viable T cells in approximately 68 mL for a target dose of 2×10^6 anti-CD19 CAR-positive viable T cells/kg body weight (range: $1 \times 10^6 – 2.4 \times 10^6$ cells/kg), with a maximum of 2×10^8 anti-CD19 CAR T cells.	Cryostor® CS10, sodium chloride; human serum albumin

7 DESCRIPTION

YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy.

YESCARTA is prepared from the patient's peripheral blood cells, which are obtained via a standard leukapheresis procedure. The mononuclear cells, which are enriched for T cells, are 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 expressing 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 transduced T cells are expanded in cell culture, washed, formulated into a suspension, and cryopreserved.

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

Appearance: YESCARTA is supplied as a cryopreserved product. The product is clear to opaque, with white to red color.

8 WARNINGS AND PRECAUTIONS

Please see the **Serious Warnings and Precautions** Box at the beginning of Part I: Health Professional Information.

General

YESCARTA should be administered in a treatment facility with personnel trained in handling and administering YESCARTA and in the management of patients treated with YESCARTA, including monitoring and managing CRS and neurotoxicity. The facility should have immediate access to appropriate emergency equipment and intensive care unit.

YESCARTA is intended solely for autologous use and should under no circumstances be administered to other patients. Before infusion, the patient's identity must match the patient identifiers on the YESCARTA infusion bag and cassette. Do NOT infuse YESCARTA if the information on the patient-specific label does not match the intended patient (see **DOSAGE AND ADMINISTRATION**).

Patients with central nervous system (CNS) lymphoma were excluded from the pivotal ZUMA-1 study. Therefore, the safety and efficacy of YESCARTA have not been established in this population. For other patient selection criteria, see **CLINICAL TRIALS**.

Patients treated with YESCARTA should not donate blood, organs, tissues and cells for transplantation.

Secondary Malignancies

Patients treated with YESCARTA may develop secondary malignancies. They should be monitored life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact the company to obtain instructions on patient samples to collect for testing.

Driving and Operating Machinery

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.

Endocrine and Metabolism

Tumour lysis syndrome (TLS)

TLS may occur in patients treated with YESCARTA. To minimize the risk of TLS, patients with elevated uric acid or high tumour burden should receive prophylactic treatment (allopurinol, or an alternative prophylaxis) prior to YESCARTA infusion.

Immune

Cytokine release syndrome (CRS)

CRS, including fatal or life-threatening reactions, occurred following treatment with YESCARTA. In ZUMA-1, CRS occurred in 93% of patients receiving YESCARTA, including ≥ Grade 3 (Lee grading system[1]) CRS in 12% of patients. 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 29 days, with the exception of one observation of 58 days). The most common manifestations of CRS (>10%) include fever (76%), hypotension (41%), tachycardia (21%), hypoxia (21%), and chills (19%). CRS can cause end organ dysfunctions. Serious events that may be associated with CRS include: cardiac arrhythmias (including atrial fibrillation/flutter and ventricular tachycardia); hypoxia; hypotension; ejection fraction decreased; cardiac arrest; cardiac failure; renal insufficiency/failure; metabolic acidosis; aspartate aminotransferase increased; alanine aminotransferase increased; blood bilirubin increased; coagulopathy; capillary leak syndrome; and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) (see **ADVERSE REACTIONS**).

In a subsequent cohort of LBCL patients, tocilizumab and/or corticosteroids were administered for ongoing Grade 1 events (see Table 2). CRS occurred in 93% of patients and 2% had Grade 3 CRS, with no patients experiencing a Grade 4 or 5 event. The median time to onset of CRS was 2 days (range: 1 to 8 days) and the median duration of CRS was 6.5 days (range: 2 to 16 days). Key manifestations of CRS (> 5%) included pyrexia, hypotension, chills, headache, nausea, tachycardia, C-reactive protein increased, fatigue, hypoxia, and vomiting.

Ensure that 4 doses of tocilizumab are available prior to infusion of YESCARTA. Monitor patients at least daily for 7 days at the specialized 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 remain within proximity of a specialized clinical facility for at least 4 weeks and to seek immediate medical attention, should signs or symptoms of CRS occur at any time (see **Monitoring and Laboratory Tests**, **WARNINGS AND PRECAUTIONS**). An algorithm has been developed to guide the management of CRS in patients treated with YESCARTA (Table 2). At the first sign of CRS, institute treatment with supportive care, tocilizumab or tocilizumab and corticosteroids as indicated.

Management of CRS

Identify CRS based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension. Manage CRS according to the recommendations in Table 2. Patients with Grade 1 CRS should be managed with vigilant supportive care and monitored for infection and fluid balance. 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. Patients with medically significant cardiac dysfunction should be managed by standards of critical care. For severe or life-threatening CRS, consider intensive care supportive therapy.

Table 2 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).	If not improving after 24 hours, administer tocilizumab per Grade 2 below.	If not improving after 3 days, administer one dose of dexamethasone 10 mg intravenously.
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 if no clinical improvement in the signs and symptoms of CRS. If improving, manage as Grade 1 above.	Administer dexamethasone 10 mg intravenously once daily. If improving, manage as Grade 1 above and continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate. If not improving, manage as appropriate grade below.
Grade 3 Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% FiO2 or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis.	Per Grade 2 If improving, manage as appropriate grade above.	Dexamethasone 10 mg intravenously three times a day. If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate. If not improving, manage as Grade 4.
Grade 4 Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD) or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2 If improving, manage as appropriate grade above.	Administer methylprednisolone 1000 mg intravenously once per day for 3 days; If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. If not improving, consider methylprednisolone 1000 mg 2-3 times a day or alternate therapy[d]

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

b. *Refer to Table 3 for management of neurologic adverse reactions.*

c. Refer to tocilizumab Product Monograph for details.

d. Alternate therapy includes (but is not limited to): anakinra, siltuximab, ruxolitinib, cyclophosphamide, intravenous immunoglobulin (IVIG) and anti-thymocyte globulin (ATG)

Hypogammaglobulinemia

B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with YESCARTA. In ZUMA-1, hypogammaglobulinemia occurred in 17% of patients. B-cell aplasia was observed in 60% and 77% of a subset of patients with evaluable blood samples at baseline and at 3 months, respectively. Monitor immunoglobulin levels after treatment with YESCARTA and manage using infection precautions, antibiotic prophylaxis and immunoglobulin replacement in case of recurrent infections.

Due to prolonged hypogammaglobulinemia and B-cell aplasia, it is not known if patients will respond to vaccination following treatment with YESCARTA. The safety of immunization with live viral vaccines during or following YESCARTA treatment has not been studied. Vaccination with live viral 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 (see **DRUG INTERACTIONS**).

Hypersensitivity reactions

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

Prolonged cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and YESCARTA infusion. In ZUMA-1, Grade 3 or higher prolonged cytopenias (still present at Day 30 or with an onset at Day 30 or beyond) included neutropenia (31%), thrombocytopenia (27%), and anemia (17%). Monitor blood counts after YESCARTA infusion.

Serious infections

Severe or life-threatening infections occurred in patients after YESCARTA infusion. In ZUMA-1, infections (all grades) occurred in 38% of patients. Grade 3 or higher infections occurred in 25% of patients including infections with an unspecified pathogen, bacterial infections, and viral infections. YESCARTA should not be administered to patients with clinically significant active 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 35% 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.

In immunosuppressed patients, life-threatening and fatal opportunistic infections including disseminated fungal infections and viral reactivation (e.g., HHV-6 and progressive multifocal leukoencephalopathy [PML]) have been reported. The possibility of these infections should be considered in patients with neurologic events and appropriate diagnostic evaluations should be performed.

Viral reactivation

Reactivation of hepatitis B virus (HBV) and human herpesvirus 6 (HHV-6) 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.

Monitoring and Laboratory Tests

- Monitor patients at least daily for 7 days at the specialized healthcare/clinical facility following infusion for signs and symptoms of CRS and neurologic adverse reactions (Table 2 and Table 3).

- CRS and neurologic adverse reactions can occur more than 7 days after the infusion. Instruct patients to remain within proximity of the specialized healthcare/clinical facility for at least 4 weeks following infusion. Educate patients and their caregivers for signs and symptoms of CRS and neurologic adverse reactions. Advise patients and their caregivers to immediately contact the designated health professional if CRS or neurologic adverse reactions are suspected.

Neurologic

Neurologic adverse reactions

Severe neurologic adverse reactions have been very commonly observed in patients treated with YESCARTA, which could be life-threatening or fatal. Neurologic adverse reactions occurred in 65% of patients, 31% of whom experienced Grade 3 or higher (severe or life threatening) adverse reactions. The median time to onset was 5 days (range 1 to 17 days). The median duration was 13 days, with a range of 1 to 191 days. Ninety-eight percent (98%) of all patients recovered from neurologic adverse reactions.

In a subsequent cohort of LBCL patients, corticosteroids were administered at the onset of Grade 1 toxicities (see Table 3). Neurologic adverse reactions occurred in 61% of patients and 17% had Grade 3 neurologic adverse reactions with no patients experiencing a Grade 4 or 5 event. The median time to onset of neurologic adverse reactions was 6 days with a median duration of 8 days (range: 1 to 144 days). The most common neurologic adverse reactions were consistent with the overall LBCL population treated with YESCARTA.

The most common signs or symptoms (>10%) associated with neurologic adverse reactions include: encephalopathy (37%); tremor (31%); confusional state (27%); aphasia (18%); and somnolence (17%). Serious adverse reactions including: encephalopathy; aphasia; delirium; seizures; spinal cord edema; myelitis; quadriplegia; and dysphagia have been reported in patients administered YESCARTA. Fatal and serious cases of cerebral edema have been reported in patients treated with YESCARTA.

Patients with a history of CNS disorders such as seizures or cerebrovascular ischemia may be at increased risk and were not enrolled in the ZUMA-1 study (see **CLINICAL TRIALS**).

Management of neurologic adverse reactions

Monitor patients for signs and symptoms of neurologic adverse reactions (Table 3). Rule out other causes of neurologic symptoms. Patients who experience Grade 2 or higher neurologic

adverse reactions should be monitored with continuous cardiac telemetry and pulse oximetry. An algorithm has been developed to guide the management of neurologic adverse reactions in patients treated with YESCARTA (Table 3). Treat moderate, severe or life-threatening neurologic adverse reactions with tocilizumab (if with concurrent CRS) and/or corticosteroids. Provide intensive care supportive therapy for severe or life threatening neurologic adverse reactions. Consider levetiracetam for seizure prophylaxis for any grade of neurologic adverse reactions. Patients should be monitored at least daily for 7 days at the specialized healthcare facility following infusion for signs and symptoms of neurologic toxicity. Counsel patients to remain within proximity of a specialized clinical facility for at least 4 weeks following infusion,and to seek immediate medical attention should signs or symptoms of neurologic toxicity occur at any time.

Table 3 Neurologic Adverse Reaction Grading and Management Guidance

Grading Assessment[a]	**Concurrent CRS**	**No concurrent CRS**
Grade 1 Examples include: Somnolence-mild drowsiness or sleepiness Confusion-mild disorientation Encephalopathy-mild limiting of ADLs	If CRS symptoms not improving after 24 hours, administer tocilizumab per Grade 2 below. Administer one dose of dexamethasone 10 mg intravenously. If not improving after 2 days, repeat dexamethasone 10 mg intravenously.	Administer one dose of dexamethasone 10 mg intravenously. If not improving after 2 days, repeat dexamethasone 10 mg intravenously.
Dysphasia-not impairing ability to communicate	Consider levetiracetam for seizure prophylaxis.	
Grade 2 Examples include: Somnolence—moderate, limiting instrumental Activities of daily living (ADL) Confusion—moderate disorientation Encephalopathy—limiting instrumental ADLs Dysphasia—moderate impairing ability to communicate spontaneously Seizure(s)	Administer tocilizumab[b] 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 if no clinical improvement in the signs and symptoms of CRS. In addition, administer dexamethasone 10 mg intravenously four times a day. If improving, continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate. If still not improving, manage as appropriate grade below.	Administer dexamethasone 10 mg intravenously four times a day. If improving, continue dexamethasone use until the severity is Grade 1 or less, then quickly taper as clinically appropriate. If still not improving, manage as appropriate grade below.

Grading Assessment[a]	Concurrent CRS	No concurrent CRS
	Consider levetiracetam for seizure prophylaxis.	
Grade 3 Examples include: Somnolence—obtundation or stupor Confusion—severe disorientation Encephalopathy—limiting self-care ADLs Dysphasia—severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly	Administer tocilizumab per Grade 2 above. In addition, administer methylprednisolone 1000 mg intravenously once daily. If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. If not improving, manage as Grade 4.	Administer methylprednisolone 1000 mg once daily. If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. If not improving, manage as Grade 4.
	Consider levetiracetam for seizure prophylaxis. Consider the possibility of cerebral edema.	
Grade 4 Life-threatening consequences Urgent intervention indicated Requirement for mechanical ventilation	Administer tocilizumab per Grade 2 above. Administer methylprednisolone 1000 mg intravenously twice per day If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. If not improving, consider 1000 mg of methylprednisolone intravenously 3 times a day or, alternate therapy.[c]	Administer methylprednisolone 1000 mg intravenously twice per day. If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. If not improving, consider 1000 mg of methylprednisolone intravenously 3 times a day or alternate therapy.[c]
	Consider levetiracetam for seizure prophylaxis. Consider the possibility of cerebral edema.	

Abbreviation: ADLs, activities of daily living.

(a) Severity based on Common Terminology Criteria for Adverse Events
(b) Refer to tocilizumab Product Monograph for details
(c) Alternate therapy includes (but is not limited to): anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG and ATG

Sexual Health

Reproduction

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. Sexually active females of reproductive potential should use effective contraception (methods that result in less than 1% pregnancy rates) after YESCARTA administration.

Sexually active males who have received YESCARTA should use a condom during intercourse with females of reproductive potential or pregnant women.

If either partner has received YESCARTA, pregnancy should be discussed with the treating physician.

See the Product Monographs 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.

Fertility

No clinical data on the effect of YESCARTA on fertility are available. Effects on male and female fertility have not been evaluated in animal studies.

8.1 Special Populations

8.1.1 Pregnant Women

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.

8.1.2 Breast-feeding

It is unknown if YESCARTA is excreted in human milk. Because many drugs are excreted in human milk, precaution should be exercised for breast-feeding. The developmental and health benefits of breast-feeding 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.

8.1.3 Pediatrics (< 18 years of age)

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

8.1.4 Geriatrics (≥ 65 years of age)

There is limited experience with YESCARTA in patients ≥ 65 years of age. Evidence from clinical studies is not sufficient to determine if the use of YESCARTA in patients ≥ 65 years of age is associated with differences in safety and effectiveness. No dose adjustment is required in patients ≥ 65 years of age.

9 ADVERSE REACTIONS

9.1 Adverse Reaction Overview

The following adverse reactions are described under **WARNINGS AND PRECAUTIONS**:

- Cytokine Release Syndrome
- Neurologic Adverse Reactions
- Hypersensitivity Reactions
- Serious Infections
- Prolonged Cytopenias
- Hypogammaglobulinemia

9.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The adverse reactions described in this section were identified in 108 adult patients with relapsed or refractory large B-cell lymphoma who received YESCARTA treatment at the recommended dose in the single arm, ongoing phase I/II study ZUMA-1 (see **CLINICAL TRIALS**). The median duration of follow-up was 15.4 months.

The most common non-hematological adverse reactions (in ≥ 20%) include: CRS (93%); fever (87%); encephalopathy (58%); hypotension (57%); tachycardia (57%); fatigue (45%); headache (44%); decreased appetite (43%); chills (37%); diarrhea (37%); hypoxia (32%); nausea (32%); tremor (31%); cough (30%); unspecified pathogen infection (28%); vomiting (26%); arrhythmia (22%); dizziness (22%); edema (21%); and constipation (20%).

Serious adverse reactions occurred in 55% of patients. The most common serious adverse reactions (≥ 2%) include: encephalopathy (19%); lung infection (7%); pyrexia (7%); pneumonia (6%); confusional state (5%); febrile neutropenia (5%); aphasia (4%); atrial fibrillation (4%); cardiac arrest (4%); urinary tract infection (4%); acute kidney injury (3%); agitation (3%); ejection fraction decreased (3%); hypotension (3%); hypoxia (3%); neutropenia (3%); somnolence (3%); atrial flutter (2%); and delirium (2%). Seventeen (16%) patients required intensive care unit admission.

The most common Grade 3 or higher adverse reactions include: encephalopathy (30%); unspecified pathogen infection (19%); hypotension (15%); fever (14%); CRS (12%); hypoxia (10%); bacterial infection (8%); aphasia (7%); arrhythmia (6%); viral infection (6%); delirium (6%); and hypertension (6%). Grade 5 (fatal) adverse events were reported in 4 patients: (anoxic brain injury [secondary to cardiac arrest which occurred in the setting of CRS]; histiocytosis haematophagic (HLH); intracranial hemorrhage in the setting of thrombocytopenia; and pulmonary embolism.

In ZUMA-1, 68% of patients received prophylactic allopurinol for TLS and 46% of patients received tocilizumab and/or corticosteroids for the treatment of adverse reactions (including CRS and neurologic adverse reactions), including 32% who required 2 or more doses of tocilizumab.

Table 4 summarizes the adverse reactions that occurred in at least 10% of patients treated with YESCARTA.

Table 4 Summary of Adverse Reactions Observed in at Least 10% of the Patients Treated with YESCARTA in ZUMA-1

Adverse Reaction	Any Grade n (%) N = 108	Grade 3 or Higher n (%) N = 108
Cardiac Disorders		
Tachycardia[a]	62 (57)	2 (2)
Arrhythmia[b]	24 (22)	6 (6)
Gastrointestinal Disorders		
Diarrhea	40 (37)	5 (5)
Nausea	35 (32)	0 (0)
Vomiting	28 (26)	1 (1)
Constipation	22 (20)	0 (0)
Abdominal pain[c]	16 (15)	2 (2)
Dry mouth	12 (11)	0 (0)
General Disorders and Administration Site Conditions		
Fever	94 (87)	15 (14)
Fatigue[d]	49 (45)	3 (3)
Chills	40 (37)	0 (0)
Edema[e]	23 (21)	1 (1)
Immune System Disorders		
Cytokine release syndrome	100 (93)	13 (12)
Hypogammaglobulinemia[f]	18 (17)	0 (0)
Infections and Infestations		
Infections-pathogen unspecified	30 (28)	20 (19)
Viral infections	21 (19)	6 (6)
Bacterial Infections	15 (14)	9 (8)
Metabolism and Nutrition Disorders		
Hypoalbunemia	106 (98)	8 (7)
Decreased appetite	46 (43)	2 (2)
Weight decreased	16 (15)	0 (0)
Dehydration	12 (11)	3 (3)
Musculoskelatal and Connective Tissue Disorders		
Motor dysfunction[g]	18 (17)	1 (1)
Pain in extremity[h]	18 (17)	1 (1)
Back pain	15 (14)	1 (1)
Muscle pain	15 (14)	1 (1)
Arthralgia	11 (10)	0 (0)
Nervous System Disorders		
Encephalopathy[i]	63 (58)	32 (30)
Headache[j]	48 (44)	1 (1)

Adverse Reaction	Any Grade n (%) N = 108	Grade 3 or Higher n (%) N = 108
Tremor	33 (31)	2 (2)
Dizziness[k]	24 (22)	1 (1)
Aphasia[l]	19 (18)	8 (7)
Psychiatric Disorders		
Delirium[m]	18 (17)	7 (6)
Anxiety	11 (10)	1 (1)
Renal and Urinary Disorders		
Renal Insufficiency	13 (12)	5 (5)
Respiratory, Thoracic and Mediastinal Disorders		
Hypoxia[p]	35 (32)	11 (10)
Cough[n]	32 (30)	0 (0)
Dyspnea[o]	21 (19)	3 (3)
Pleural effusion	14 (13)	2 (2)
Vascular Disorders		
Hypotension[q]	62 (57)	16 (15)
Hypertension	16 (15)	6 (6)

The following events were also counted in the incidence of CRS: tachycardia, arrhythmia, fever, chills, hypoxia, renal insufficiency, and hypotension. MedDRA version 19.0, CTCAE version 4.03.

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, localized 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. *Cough includes cough, productive cough, upper-airway cough syndrome.*
o. *Dyspnea includes acute respiratory failure, dyspnea, orthopnea, respiratory distress.*
p. *Hypoxia includes hypoxia, oxygen saturation decreased.*
q. *Hypotension includes diastolic hypotension, hypotension, orthostatic hypotension.*

No new safety concerns were identified in the 24-month analysis, which included a median duration of follow-up of 27.4 months.

9.3 Less Common Clinical Trial Adverse Reactions

Other clinically important adverse reactions (any grade) 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%); ejection fraction decreased (4%);
- *Immune system disorders*: Hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) (1%), hypersensitivity (1%);
- *Infections and infestations disorders:* Fungal infections (6%); human herpesvirus 6 infection (1%);
- *Metabolism and nutrition disorders:* metabolic acidosis (5%);
- *Nervous system disorders:* Ataxia (6%); neuropathy (4%); seizure (4%); dyscalculia (2%); and myoclonus (2%);
- *Respiratory, thoracic and mediastinal disorders:* Pulmonary edema (9%);
- *Skin and subcutaneous tissue disorders:* Rash (3%); and
- *Vascular disorders:* Thrombosis (6%); capillary leak syndrome (3%)

9.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Table 5 describes the laboratory abnormalities of Grade 3 or 4 that occurred in at least 10% of patients in ZUMA-1.

Table 5 Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Patients in ZUMA-1 Following Treatment with YESCARTA based on CTCAE (N=108)

Lab Abnormality	Grades 3 or 4 n (%)
Lymphopenia	107 (99)
Leukopenia	104 (96)
Neutropenia	100 (93)
Anemia	68 (63)
Thrombocytopenia	61 (56)
Hypophosphatemia	56 (52)
Hypokalemia	34 (32)
Hyponatremia	25 (23)
Uric Acid increased	16 (15)
Direct bilirubin increased	14 (13)
Alanine Aminotransferase increased	13 (12)
Aspartate aminotransferase increased	11 (10)

Immunogenicity

YESCARTA has the potential to induce anti-product antibodies, which 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. In ZUMA-1, 3% of patients (3 out of 101) evaluated showed low levels of anti FMC63 antibodies at baseline without titre elevation post treatment. No patients developed *de novo* antibodies against FMC63. There is no evidence that the kinetics of expansion of YESCARTA, or the safety or effectiveness of YESCARTA, was altered in these patients.

9.5 Post-Market Adverse Reactions

In addition to adverse reactions from clinical studies, the following adverse reactions were identified during post-marketing use of YESCARTA. Because these reactions were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Nervous System Disorders

Spinal cord edema, myelitis, quadriplegia, and dysphagia (see **WARNINGS AND PRECAUTIONS**).

10 DRUG INTERACTIONS

10.1 Overview

No formal interaction studies have been performed with YESCARTA.

10.2 Drug-Drug Interactions

Pharmacokinetic Interactions

No pharmacokinetic drug interaction studies have been performed with YESCARTA.
T-cells are known to be susceptible to immune-suppressive agents. The benefit/risk of immuno-suppressive agents including but not limited to corticosteroids, cytotoxic chemotherapy, immunophilins, mTOR inhibitors, should be considered as these can be lymphotoxic and may reduce the effectiveness of YESCARTA (see **ACTION AND CLINICAL PHARMACOLOGY** - **Pharmacokinetics**).

Pharmacodynamic Interactions

The immunization with vaccines during or following YESCARTA treatment has not been studied. The effectiveness of vaccines may be affected by prolonged B-cell aplasia and hypogammaglobulinemia (see **WARNINGS AND PRECAUTIONS**). The safety of live viral vaccines has not been investigated in patients treated with YESCARTA; vaccination with live viral 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.

11 ACTION AND CLINICAL PHARMACOLOGY

11.1 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 elimination of CD19-expressing cells.

11.2 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, YESCARTA treatment can result in a period of B-cell aplasia and hypogammaglobulinemia.

Among evaluable subjects with an ongoing response at 24 months, 46% had no detectable B cells at baseline, and a majority of subjects at Month 3 (79%) and Month 6 (78%) had no detectable B cells. Among evaluable subjects who had relapsed by 24 Months, 63% had no detectable B cells at baseline, and a majority of subjects at Month 3 (63%) and Month 6 (70%) had no detectable B cells. At Month 24, 74% of subjects with an ongoing response and 100% of subjects who relapsed had detectable B cells.

11.3 Pharmacokinetics

Following infusion of YESCARTA in adult patients with large B-cell lymphoma, 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.

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 C_{max} levels in responders (n=71) were 216% of the corresponding level in nonresponders (n=27) (43.6 cells/μL vs 20.2 cells/μL). Median AUC Day 0-28 in responding patients (n=71) was 253% of the corresponding level in nonresponders (n=27) (561.96 days × cells/μL vs. 222.04 days × cells/μL).

Table 6 Cellular Kinetic parameters of YESCARTA in adult patients with relapsed or refractory large B-cell lymphoma

Parameter n, Median (Min, Max)	Responding Patients N = 73	Non-Responding Patients N = 28
Peak (cells/μL)	n=71, 43.55 (0.84, 1513.69)	n=27, 20.2 (1.25, 167.42)
T_{max} (day)	n=71, 8 (8, 29)	n=27, 8 (8, 78)
Median $AUC_{0\text{-}28d}$ (days x cells/ μL)	n=71, 561.96 (14.44, 14329.29)	n=27, 222.04 (5.09, 2112.82)
Median $AUC_{0\text{-}90d}$ (days x cells/ μL)	n=72, 697.31 (14.44, 15940.07)	n=27, 303.9 (5.09, 6420.66)

N is equal to the total number of patients and n is the number of patients with evaluable PK parameter.
Response data are based on central read per Cheson 2007.
Peak is defined as the maximum number of CAR T cells measured post infusion.
Area under curve (AUC) is defined as the area under curve in a plot of number of CAR T cells against scheduled visit from Day 0 to Day 28 (or from Day 0 to Day 90).
Time-to-peak is defined as number of days from YESCARTA infusion to the date when the CAR T cells in blood firstly reached the maximum post-baseline level.

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

Hepatic and renal impairment studies of YESCARTA were not conducted.

12 STORAGE, STABILITY AND DISPOSAL

Storage

- YESCARTA must be stored in the VAPOUR PHASE of liquid nitrogen (≤ -150°C) and it must remain frozen until the patient is ready for treatment to assure viable live autologous cells are available for patient administration.
- Thawed product should NOT be refrozen.

Stability

- Final product is stable for 18 months when stored frozen in the vapour phase of liquid nitrogen.
- Final product is stable for up to 3 hours after thawing.

Disposal

- Unused medicine must be disposed of in compliance with local guidelines for the disposal of medicinal products containing blood borne pathogens and genetically modified cells.

13 SPECIAL HANDLING INSTRUCTIONS

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

PART II: SCIENTIFIC INFORMATION

14 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: axicabtagene ciloleucel

Physicochemical properties: axicabtagene ciloleucel is a clear to opaque, white to red suspension of cells for infusion.

Product Characteristics

YESCARTA is prepared from the patient's peripheral blood cells, which are obtained via a standard leukapheresis procedure. The mononuclear cells, which are enriched for T cells, are 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 ADMINISTATION, STORAGE, STABILITY AND DISPOSAL, SPECIAL HANDLING INSTRUCTIONS**).

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

15 CLINICAL TRIALS

Relapsed or Refractory Large B-Cell Lymphoma

15.1 Trial Design and Study Demographics

Table 7 Summary of Patient Demographics for the Clinical Trial in Relapsed or Refractory Large B-Cell Lymphoma

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex n (%)
ZUMA-1 (Phase 2)	Single-arm, open-label, multicenter trial in adult patients with relapsed or refractory large B-cell lymphoma	Single intravenous infusion of YESCARTA at a target dose of 2×10^6 CAR-positive viable T cells/kg (maximum permitted dose: 2×10^8 cells)	111 patients underwent leukapheresis; 103 patients treated with conditioning chemotherapy; 101 received YESCARTA	Leukapheresed and Treated groups: 56 years (range: 23 to 76)	Leukapheresed: 77 (69%) males 34 (31%) females Treated: 68 (67%) males 33 (33%) females

ZUMA-1 is a single-arm, open-label, Phase I/II, multicenter trial that evaluated the efficacy and safety of a single infusion of YESCARTA in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma (large B-cell lymphoma) after two or more lines of systemic therapies. Eligible patients had refractory disease to the most recent therapy or relapse within 1 year after autologous hematopoietic stem cell transplantation (HSCT). Prior therapies must include anti-CD20 antibody therapy and an anthracycline-containing regimen.

The study excluded patients with prior allogeneic HSCT or CD19-targeting CAR therapy, central nervous system (CNS) lymphoma or a history of other CNS disorders (such as seizures or cerebrovascular ischemia), thrombolic events in the last 6 months, Eastern Cooperative Oncology Group (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 room air oxygen saturation of less than 92%, active serious infection or active autoimmune disease requiring systemic immunosuppression.

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 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 5th, 4th, and 3rd day before YESCARTA. No bridging chemotherapy was permitted in the study. All patients were hospitalized for YESCARTA infusion and for a minimum of 7 days afterward.

Of the 111 patients who underwent leukapheresis, 103 patients received conditioning chemotherapy and 101 received YESCARTA (Table 7). Of the 10 patients who underwent leukapheresis but did not receive YESCARTA, 1 was due to manufacturing failure and 9 were due to progressive disease or serious adverse events prior to YESCARTA infusion. 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).

Of the 101 patients treated with YESCARTA, the median age was 58 years (range: 23 to 76), 67% were male, and 86% were white. The baseline ECOG performance status was 42% with ECOG 0, and 58% with ECOG 1. The median number or prior therapies was 3 (range: 1 to 10), 76% of patients had refractory disease to 2 or more lines of therapy, and 21% had relapsed within 1 year of autologous HSCT. There were 46% of patients with International Prognostic Index 3/4 and 85% with disease stage III/IV. Seventy-seven patients had histologically confirmed DLBCL, 8 had PMBCL and 16 had DLBCL arising from follicular lymphoma, based on the 2008 WHO-classification. DLBCL in ZUMA-1 included patients with DLBCL not otherwise specified (NOS), other DLBCL subtypes, and high-grade B-cell lymphoma (HGBCL) based on the 2016 WHO-classification. Forty patients were evaluable for myelocytomatosis viral oncogene homolog (MYC), B-cell lymphoma-2 (BCL-2), and BCL-6 status. Twenty-seven were found to have double expressor DLBCL (overexpression of both MYC and BCL-2 protein); 4 were found to have HGBCL with MYC, BCL-2, or BCL-6 gene rearrangement (double- and triple-hit); and 2 were found to have HGBCL not otherwise specified. Sixty six patients were evaluable for cell-of-origin classifications (germinal center B-cell type [GCB] or activated B-cell type [ABC]). Of these, 49 patients had GCB-type and 17 patients had ABC-type.

The efficacy of YESCARTA was evaluated in the modified intent-to-treat (mITT) population defined as all patients who received YESCARTA (Table 8). The primary efficacy endpoint was objective response rate (ORR).

15.2 Study Results

Table 8 Summary of Efficacy Results for ZUMA-1 Phase 2 (Primary Analysis; 6 months; independent review) in relapsed or refractory large B-cell lymphoma (mITT population)

Efficacy Endpoints	N =101
Objective Response Rate [a], n (%) (95% CI)	73 (72%) (62, 81)
Complete Remission Rate, n (%) (95% CI)	52 (51%) (41, 62)
Partial Remission Rate, n (%) (95% CI)	21 (21%) (13, 30)
DOR (months)[b] Median[c] (95% CI) Range[d] Probability at 6 months[c] (95% CI)	 9.2 (5.4, NE) 0.0+, 14.4+ 62.0% (48.9%, 72.7%)
DOR if Best Response is CR (months) Median[c] (95% CI) Range[d]	 NE (8.1, NE) 0.4, 14.4+
DOR if Best Response is PR (months) Median[c] (95% CI) Range[d]	 2.1 (1.3, 5.3) 0.03+, 8.4+
Median Follow-up for DOR (Months)[b,c] (95% CI)	7.9 (6.2, 9.6)

CI, confidence interval; CR, complete remission; DOR, duration of response; NE, not estimable; PR, partial remission; SCT, stem cell transplant.

[a] *The objective response was assessed per the revised International Working Group response criteria, Cheson BD et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007 Feb 10;25(5).*

[b] *Among all responders. DOR is measured from the date of first objective response to the date of progression or death from relapse or toxicity. DOR was censored for 60% of patients who achieved a CR or PR, including those who received a new therapy, had SCT, or had an ongoing response. DOR was censored at the time of SCT for patients who received SCT while in response.*

[c] *Kaplan-Meier estimate.*

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

Among the 101 patients included in the primary analysis, the best ORR was 72% (73/101) (95% confidence interval [CI]: 62, 81). Fifty-two patients (51%) achieved a complete remission (CR) and 21 patients (21%) achieved partial remission (PR). The median DOR was 9.2 months (95%CI: 5.4, NE). The median time to response was 0.9 months (range: 0.8 to 6.2 months). The DOR was longer in patients who achieved CR, as compared to patients with a best response of PR (Table 8).

Table 9 Summary of Efficacy Results for ZUMA-1 Phase 2 (12-month Analysis; independent review) in relapsed or refractory large B-cell lymphoma (mITT population)

Efficacy Endpoints	N =101
Objective Response Rate [a], n (%)	73 (72%)

Efficacy Endpoints	N =101
(95% CI)	(62, 81)
Complete Remission Rate, n (%)	52 (51%)
(95% CI)	(41, 62)
Partial Remission Rate, n (%)	21 (21%)
(95% CI)	(13, 30)
DOR (months)[b]	
Median[c]	14.0
(95% CI)	(8.3, NE)
Range	0.0+, 17.3+
Probability at 12 months[c] (95% CI)	52.7% (38.6%, 65.0%)
DOR if Best Response is CR (months)	
Median[c]	NE
(95% CI)	(11.3, NE)
Range	0.4, 17.3+
DOR if Best Response is PR (months)	
Median[c]	2.1
(95% CI)	(1.3, 5.3)
Range	0.0+, 12.1+
Median Follow-up for DOR (Months)[b,c]	11.1
(95% CI)	(10.8, 13.6)

CI, confidence interval; CR, complete remission; DOR, duration of response; NE, not estimable; PR, partial remission; SCT, stem cell transplant.

[a]The objective response was assessed per the revised International Working Group response criteria, Cheson BD et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007 Feb 10;25(5).

[b]Among all responders. DOR is measured from the date of first objective response to the date of progression or death from relapse or toxicity. DOR was censored for 59% of patients who achieved a CR or PR, including those who received a new therapy, had SCT, or had an ongoing response. DOR was censored at the time of SCT for patients who received SCT while in response.

[c]Kaplan-Meier estimate.

[d]A + sign indicates a censored value.

In the 12-month follow-up analysis, the ORR was 72% (73/101) (95% CI: 62, 81). Fifty-two patients (51%) achieved a CR and 21 patients (21%) achieved a PR. The median DOR was 14 months (95% CI: 8.3, NE). The median time to response was 1.0 months (range: 0.8 to 6.3 months). The DOR was longer in patients who achieved CR, as compared to patients with a best response of PR (Table 9).

In the 24 month follow-up analysis of ZUMA-1 Phase 2 (independent review; mITT population), the ORR was 74% (75/101) with a median follow-up time of 27.1 months. Fifty-five patients (54%) achieved a CR and 20 patients (20%) achieved a PR. The median DOR was not reached (median follow-up for DOR was 22.9 months). The median time to response was 1.0 month (range: 0.8 to 12.2 months). The DOR was longer in patients who achieved CR, as compared to patients with a best response of PR. Of the 55 patients who achieved CR, 7 patients had stable disease (SD) and 10 had PR at their initial tumor assessment and converted to CR as late as 15.3 months after YESCARTA infusion.

In a subsequent, open label, safety management cohort in ZUMA-1 that evaluated the safety and efficacy of YESCARTA with the use of corticosteroids and/or tocilizumab for Grade 1 CRS or neurologic events (see Table 2 and Table 3), a total of 46 patients with relapsed or refractory LBCL were enrolled and 41 patients were treated with YESCARTA. The efficacy outcomes observed in this cohort were comparable to the efficacy outcomes of the ZUMA-1 pivotal cohorts.

16 MICROBIOLOGY

Not applicable.

17 NON-CLINICAL TOXICOLOGY

YESCARTA comprises engineered human T-cells, therefore there are no representative *in vitro* assays, *ex vivo* models, or *in vivo* models that can accurately address the toxicological characteristics of the human product. Hence, traditional toxicology studies used for drug development were not performed.

No carcinogenicity or genotoxicity studies have been conducted with YESCARTA.

No studies evaluating the effects of YESCARTA on fertility, reproduction and development have been conducted.

18 SUPPORTING PRODUCT MONOGRAPHS

1) PrACTEMRA (tocilizumab, 20 mg/mL [Concentrate Solution for Infusion]; 162 mg/0.9 mL [Solution for Injection], Hoffmann-La Roche Limited, Submission Control 198824, Product Monograph, Aug. 30, 2017.
2) PrFludarabine Phosphate, Teva Canada Limited. Fludarabine Phosphate Sterile Solution for Injection 25 mg/mL (2 mL per vial). Product Monograph. Toronto, Canada. Date of Revision: 01 March. 2016.
3) PrPROCYTOX Cyclophosphamide, Baxter Corporation. PrPROCYTOX Cyclophosphamide Tablets USP: 25 mg, 50 mg Cyclophosphamide for injection: 200 mg, 500 mg, 1000 mg, 2000 mg (powder for injection) per vial. Product Monograph. Mississauga, Ontario. Date of Revision: 07 September. 2012.
4) PrAPO-PREDNISONE, Apotex Inc. PrAPO-PREDNISONE Prednisone Tablets USP 1 mg, 5 mg and 50 mg. Canadian Prescribing Information. Toronto, Canada. Date of Revision: 28 May. 2015.
5) PrDEXAMETHASONE OMEGA UNIDOSE, Omega Laboratories Limited. PrDEXAMETHASONE OMEGA UNIDOSE (Dexamethasone Sodium Phosphate Injection USP) (10 mg/mL). Montreal, Quebec, Canada. Date of Preparation: 12 June. 2012.
6) Pr ZYLOPRIM®, AA Pharma Inc. Allopurinol tablets, 100, 200, and 300 mg. Product Monograph. Vaughan, Ontario Canada. Date of Preparation: 15 September 2010.
7) PrKINERET® (anakinra, solution for injection, 150 mg/mL). Swedish Orphan Biovitrum AB. Product Monograph. Stockholm, Sweden. Date of Approval : March 28, 2018.
8) PrSYLVANT® (siltuximab for injection; 100 mg/vial and 400 mg/vial). Janssen Inc. Product Monograph. Toronto, Ontario, Canada. Date of Approval: 16 March 2018.
9) PrJAKAVI® (ruxolitinib tablets; 5 mg, 10 mg, 15 mg and 20 mg). Novartis Pharmaceuticals Canada Inc. Product Monograph. Dorval, Quebec, Canada. Date of Revision: September 28, 2018.
10) GAMMAGARD LIQUID (Immune Globulin Intravenous [IVIG] 10% Solution for Infusion), Shire Pharma Canada ULC. Toronto, Ontario, Canada. Product Monograph. Date of Approval: May 4, 2018.
11) PrATGAM® (anti-thymocyte globulin [equine]). Pfizer Canada Inc. Concentrate for solution for infusion / sterile solution - 50 mg/mL). Product Monograph. Kirkland, Quebec, Canada. Date of Revision: 28 May 2014.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Yescarta®
(axicabtagene ciloleucel)
Suspension for Intravenous Infusion

*Read this carefully before you start taking **Yescarta** (pronounced yes-kar-ta). This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Yescarta**.*

Serious Warnings and Precautions

Yescarta can cause serious side effects that are life-threatening. Sometimes, these serious side effects that are life-threatening can lead to death. The serious adverse effects of **Yescarta** include the following:

- **Cytokine release syndrome (CRS):** if you have CRS, you may experience one or more of the following symptoms: chills; high fever; feeling weak or very tired; nausea, vomiting; diarrhea; muscle or joint pain; dizziness; headache; cough; shortness of breath; and fast or irregular heartbeat. Talk to your healthcare professional immediately if you have any of these symptoms.
- **Neurologic side effects:** if you have serious neurologic side effects, you may experience one or more of the following symptoms: fit; shaking; difficulty speaking or swallowing; dizziness; confusion; delirium; memory loss, seizure; loss of balance; and decreased or loss of consciousness. Talk to your healthcare professional immediately if you have any of these symptoms.

You will only be given **Yescarta** by an experienced healthcare professional at specialized treatment centers.

What is Yescarta used for?

- **Yescarta** is a treatment for your large B-cell lymphoma – a form of white blood cell cancer. It is used when you have failed at least two other kinds of treatment.

How does Yescarta work?

Yescarta is made from your own white blood cells. Some of these cells are taken from your body and then genetically modified to make **Yescarta**. **Yescarta** is given to you by drip (infusion) into a vein. **Yescarta** recognizes and attacks your lymphoma cells.

What are the ingredients in Yescarta?

- Medicinal ingredients: axicabtagene ciloleucel
- Non-medicinal ingredients: Cryostor® CS10, sodium chloride, human serum albumin

Yescarta comes in the following dosage forms:

Yescarta comes as a cell suspension in one infusion bag. The entire content of the bag should be given to you by drip into a vein as a single, one-time treatment.

Do not use Yescarta if:

- You are allergic to **Yescarta** or any of the other ingredients of this medicine (Read "What are the ingredients in **Yescarta**?" above).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Yescarta. Talk about any health conditions or problems you may have, including if you

- Have a brain tumour or any other types of cancer.
- Have had a stem cell transplant or any other organ transplant in the past.
- Have or have had problems with the heart, blood pressure, lung, liver or kidney.
- Have had blood clots in the body.
- Have any symptoms of CRS (severe systemic inflammation), such as chills, high fever, feeling weak or very tired, nausea, vomiting, diarrhea, muscle or joint pain, dizzy, headache, cough, shortness of breath, or fast or irregular heartbeat.
- Have any symptoms of neurologic problems, such as fits, stroke, shaking, difficulty speaking or swallowing, confusion, delirium, memory loss, seizure, loss of balance, loss of consciousness or decreased level of consciousness.
- Have any symptoms of infection, such as fever (100.4°F/38°C), chill, sore throat, coughing, chest pain, stomach pain, vomiting, and diarrhea.
- Have any symptoms of low red blood cells, such as feeling weak or very tired, and shortness of breath.
- Have any symptoms of low platelets (a type of blood cell), such as bleeding or bruising more easily.
- Had or have hepatitis B or C or HIV (human immunodeficiency virus).
- Had a vaccine in the previous 6 weeks or are planning to have one in the next few months.
- Have any symptoms of severe allergic reactions, such as shortness of breath or trouble breathing, skin rash, swelling of the lips, tongue, or face, chest pain, feeling dizzy or faint.
- Have any symptoms of tumour lysis syndrome, such as nausea, vomiting, diarrhea, muscle cramps or twitches, weakness, numbness or tingling, feeling tired, less urine, irregular heartbeat, confusion, restless, delirium or seizure.
- Are pregnant, think you are pregnant or plan to become pregnant.
- Are a man and you plan to father a child after **Yescarta** treatment.
- Are breast-feeding or plan to do so.

Other warnings you should know about:

- Do not drive, use heavy machinery, or do other dangerous things for 8 weeks after you get **Yescarta** because the treatment can cause sleepiness, confusion, weakness, memory and coordination problems.
- Do not donate blood, organs, tissues and cells for transplantation after **Yescarta** treatment.
- Cases of PML have been reported following **Yescarta** use. PML is a rare brain infection that can be fatal. Tell your doctor right away if you notice or someone notices in you: progressive

weakness on one side of the body; clumsiness of limbs; disturbance of vision; changes in thinking; memory and orientation; confusion; or personality changes. Your doctor may request further testing if PML is suspected.

Tell your doctor about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.
The following may interact with Yescarta:

- Corticosteroids, chemotherapy, and other medications that can suppress your immune system: they may make **Yescarta** less effective.
- Vaccines: **Yescarta** may make some vaccines less effective. It may not be safe for you to receive a live viral vaccine (a type of vaccine made from weakened virus) during or shortly after **Yescarta**.

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 remove some of your white blood cells and concentrate them.
- 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 professional will give it to you through a catheter placed into your vein (intravenous infusion). The treatment usually takes less than 30 minutes.
- You will be monitored where you received your **Yescarta** daily for at least 7 days after the treatment. You should plan to stay close to the location where you received your treatment for at least 4 weeks after getting **Yescarta**. Your healthcare professional will help you with any side effects that may occur.
- You may be hospitalized for side effects and your healthcare professional will discharge you if your side effects are under control, and it is safe for you to leave the hospital.
- Your doctor will give you a **Patient Alert Card**. Read it carefully and follow the instructions on it.
- Always show the Patient Alert Card to the doctor or nurse when you see them or if you go to hospital.
- Your healthcare professional 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 professional as soon as possible to reschedule.

Usual dose:

Yescarta comes as a cell suspension in one infusion bag. The target dose is 2×10^6 manufactured live T-cells (that is CAR T-cells) per kg body weight; with a maximum of 2×10^8 CAR T-cells (if you weigh 100 kg or higher). The entire content of the bag should be given to you as a single, one-time treatment.

What are possible side effects from using Yescarta?

These are not all the possible side effects you may feel when taking **Yescarta**. If you experience any side effects not listed here, contact your healthcare professional.

Very common:

- Low blood pressure, dizziness
- Headache, difficulty in speaking, agitation, shaking, feeling sick, constipation, diarrhea, pain in the stomach or being sick
- Shortness of breath, cough
- Low levels of antibodies called immunoglobulins, which may lead to infections
- Muscle pains, back pain
- Extreme tiredness
- Dehydration

Common:

- Difficulty understanding numbers, memory loss
- Muscle spasms
- Swelling
- Rash
- Itching

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
High fever, chills, difficulty breathing, nausea, vomiting, diarrhea, muscle pain, joint pain, low blood pressure, or dizziness/light headedness (possible symptoms of cytokine release syndrome [CRS])		✓	✓
Fits (seizures), shaking, loss/decreased level of consciousness, confusion, loss of balance or coordination, difficulty self-caring, difficulty reading, writing, and understanding (possible symptoms of neurologic problems)		✓	✓
Feeling warm, fever, chills or shivering; depending on the location of infection, you may also experience cough, difficulty breathing, painful urine or blood in urine, sore throat, or chest pain (possible symptom of infections)		✓	
Weakness, loss of energy, rapid heartbeat, shortness of breath, pale skin, low level of red blood cells in blood test (possible symptoms of low level of red blood cells)		✓	
Spontaneous bleeding or bruising (possible symptoms of low levels of blood platelets or thrombocytopenia)		✓	
COMMON			
Low number of white blood cells in your blood test; you may or may not have an infection at the same time (neutropenia or febrile neutropenia)		✓	

Changes in functioning or rhythm of the heart (atrial fibrillation, atrial flutter, or ejection fraction decreased)		✓	
Breathlessness, difficulty breathing when lying down (possible symptoms of heart failure)		✓	✓
Loss of consciousness, loss of heartbeat (possible symptoms of cardiac arrest)		✓	✓
Very little or no urine (possible symptoms of acute kidney injury)		✓	
Being anxious, nervous		✓	
Dizziness, light headedness caused by low blood pressure (hypotension)		✓	
Headache or dizziness caused by high blood pressure (hypertension)		✓	
Shortness of breath, fast heartbeat, blue discoloration of lips or extremities (possible symptoms of hypoxia)		✓	
Chest pain, cough, shortness of breath, caused by fluid around the lungs (pleural effusion)		✓	
Extreme shortness of breath or difficulty breathing, feeling suffocated, anxious, restless, cough, frothy sputum with or without blood, blue colored lips, or fast heartbeat, caused by fluid in the lungs (possible symptoms of pulmonary edema)		✓	✓
Leakage of fluids from blood vessels into surrounding tissue (capillary leak syndrome)		✓	
Feeling very tired (somnolence)		✓	
State of severe confusion (delirium)		✓	✓
Extreme activation of the immune system with fever, rash and injury to liver, blood cells and brain (histocytosis hematophagic)		✓	✓
Spontaneous or prolonged and excessive bleeding (coagulopathy)		✓	✓
Blood clots that lower blood flow (thrombosis)		✓	
Reduced level of sodium in the blood, sometimes leading to nausea, headache, drowsiness, restlessness, irritability muscle weakness and cramps (hyponatremia)		✓	
Reduced level of phosphate in the blood, sometime leading to muscle weakness (hypophosphatemia)		✓	
Reduced levels of potassium in the blood, possibly leading to muscle weakness, muscle spasms, abnormal heart rhythm (hypokalemia)		✓	
Nausea, vomiting, fast breathing, and lethargy caused by high levels of acid in the blood (metabolic acidosis)		✓	
Difficulty to swallow (dysphagia)		✓	✓
RARE			
Inflammation and swelling of spinal cord which may cause partial or total paralysis of limbs and torso (myelitis, spinal cord edema and quadriplegia)		✓	✓

Progressive weakness on one side of the body, clumsiness of limbs, disturbance of vision, changes in thinking, memory and orientation, confusion, personality changes (Progressive multifocal leukoencephalopathy [PML])		✓	✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

If you want more information about Yescarta:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.gilead.ca, or by calling 1-866-207-4267.

This leaflet was prepared by Gilead Sciences Canada, Inc.

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