PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PR TECARTUS™

Brexucabtagene autoleucel

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 anti-CD19 CAR-positive viable T cells or target of 1×10^6 chimeric antigen receptor (CAR)-positive viable T cells per kg body weight with a maximum of 1×10^8 anti-CD19 CAR-positive viable T cells, for intravenous infusion

Professed Standard

Other antineoplastic agent (Anatomical Therapeutic Chemical index code: L01XX)

Kite Pharma Inc.
Santa Monica, CA 90404

Manufactured for:
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RECENT MAJOR LABEL CHANGES

Indications (1)	11/2022
Serious Warnings and Precautions Box (3)	11/2022
Dosage and Administration (4.2)	11/2022
Warnings and Precautions, Immune (7)	11/2022
Warnings and Precautions, Neurologic (7)	11/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TECARTUS (brexucabtagene autoleucel suspension for intravenous infusion) is a CD19-directed genetically modified autologous T cell immunotherapy indicated for:

- the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.
- the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

1.1 Pediatrics

The safety and efficacy of TECARTUS in patients < 18 years of age have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

In MCL, evidence from clinical studies suggest that efficacy and safety in patients ≥ 65 years of age were consistent with the overall treated patient population.

In ALL, evidence from clinical studies is not sufficient to determine if the use of TECARTUS in patients ≥ 65 years of age is associated with differences in safety and effectiveness.

2 CONTRAINDICATIONS

TECARTUS 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 and life-threatening reactions, occurred in patients receiving TECARTUS. Do not administer TECARTUS 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 TECARTUS. Provide supportive care, tocilizumab, or tocilizumab and corticosteroids, as needed (see **WARNINGS AND PRECAUTIONS**).
- **Neurologic adverse reactions**, including fatal and life-threatening reactions, occurred in patients receiving TECARTUS, including concurrently with CRS or independently of CRS. Monitor for neurologic adverse reactions after treatment with TECARTUS. Provide supportive care, tocilizumab (if with concurrent CRS), or corticosteroids, as needed (see **WARNINGS AND PRECAUTIONS**).
- TECARTUS should be administered by experienced health professionals at specialized treatment centres (see **WARNINGS AND PRECAUTIONS**).

4 DOSAGE AND ADMINISTRATION

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

4.1 Dosing Considerations

- For intravenous (IV) use only
- Single infusion product
- For autologous use only; do NOT infuse TECARTUS if the information on the patient-specific label on the infusion bag does not match the intended patient.
- Do not use a leukodepleting filter.
- Do not irradiate TECARTUS.
- Due to the risks associated with TECARTUS, consider delaying lymphodepleting chemotherapy and TECARTUS 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

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

Recommended Dosage for MCL

Each single infusion bag of TECARTUS contains a suspension of anti-CD19 chimeric antigen receptor (CAR)-positive T cells in approximately 68 mL. The target dose is 2 x 10^6 anti-CD19 CAR-positive viable T cells per kg body weight (range: 1 x 10^6 – 2 x 10^6 CAR-positive viable T cells/kg), with a maximum of 2 x 10^8 CAR-positive viable T cells for patients 100 kg and above.

Recommended Dosage for ALL

Each single infusion bag of TECARTUS contains a suspension of anti-CD19 CAR-positive viable T cells in approximately 68 mL. The target dose is 1 × 10^6 anti-CD19 CAR-positive viable T cells per kg body weight, with a maximum of 1 × 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 Reconstitution

Not applicable.

4.4 Administration

TECARTUS is for autologous use only. The patient's identity must match the patient identifiers on the TECARTUS cassette and infusion bag. Do NOT infuse TECARTUS 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 TECARTUS Infusion

Confirm availability of TECARTUS prior to starting the lymphodepleting chemotherapy regimen.

Pre-treatment *(lymphodepleting chemotherapy)*

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

- ALL: Administer a lymphodepleting chemotherapy regimen of fludarabine 25 mg/m^2 intravenously over 30 minutes on the 4th, 3rd, and 2nd day and cyclophosphamide 900 mg/m^2 intravenously over 60 minutes on the 2nd day before infusion of TECARTUS.

Premedication

- Administer acetaminophen 650 mg orally and diphenhydramine 12.5 to 25 mg intravenously or 25 mg orally approximately 1 hour before TECARTUS infusion.
- AVOID prophylactic use of systemic corticosteroids, as it may interfere with the activity of TECARTUS.

Preparation of TECARTUS for Infusion

- Coordinate the timing of TECARTUS thaw and infusion. Confirm the infusion time in advance, and adjust the start time of TECARTUS thaw such that it will be available for infusion when the patient is ready.
- Confirm patient identity: Prior to TECARTUS preparation, match the patient's identity with the patient identifiers on the TECARTUS cassette.
- Do NOT remove the TECARTUS 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 TECARTUS product bag from the cassette and check that the patient information on the cassette label matches the bag label.
- Inspect the infusion 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 the infusion bag 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 TECARTUS in new media prior to infusion. Thawing should take approximately 3-5 minutes.
- Once thawed, TECARTUS should be administered within 30 minutes but 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 administration of TECARTUS.
- Confirm the patient's identity matches the patient identifiers on the TECARTUS infusion bag.
- Prime the tubing with 0.9% sodium chloride solution prior to infusion.
- Infuse the entire content of the TECARTUS bag within 30 minutes by either gravity or a peristaltic pump. TECARTUS 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 TECARTUS 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 TECARTUS is delivered.

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	MCL: Each patient-specific, single infusion bag of TECARTUS 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: $1 \times 10^6 – 2 \times 10^6$ CAR-positive viable T cells/kg), with a maximum of 2×10^8 anti-CD19 CAR-positive viable T cells. ALL: Each patient-specific, single infusion bag of TECARTUS contains a suspension of anti-CD19 CAR-positive viable T cells in approximately 68 mL for a target dose of 1×10^6 CAR-positive viable T cells/kg body weight, with a maximum of 1×10^8 anti-CD19 CAR-positive viable T cells.	Cryostor®, sodium chloride; human serum albumin

7 WARNINGS AND PRECAUTIONS

Please see the **SERIOUS WARNINGS AND PRECAUTIONS BOX** at the beginning of Part I: Health Professional Information.

General

TECARTUS should be administered in a treatment facility with personnel trained in handling and administering TECARTUS and in the management of patients treated with TECARTUS, including monitoring and managing cytokine release syndrome and neurologic adverse reactions. The facility should have immediate access to appropriate emergency equipment and intensive care unit.

TECARTUS 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 TECARTUS infusion bag and cassette. Do not infuse TECARTUS if the information on the patient-specific label does not match the intended patient (see **DOSAGE AND ADMINISTRATION**).

Patients with central nervous system (CNS) involvement were excluded from the pivotal ZUMA-2 (MCL) and ZUMA-3 (ALL) studies. Therefore, the safety and efficacy of TECARTUS have not been established in these populations. Patients who had received a prior allogeneic stem cell transplant were excluded from the pivotal ZUMA-2 study due to the potential risk for TECARTUS to aggravate graft-versus-host disease (GvHD). In ZUMA-3, 37% of ALL patients had received prior allogeneic stem cell transplant prior to TECARTUS infusion and GvHD was observed after TECARTUS infusion in 6% of patients (2/55 patients in Phase 2 and 3/23 patients in Phase 1). For other patient selection criteria, see **CLINICAL TRIALS**.

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

Secondary Malignancies

Patients treated with TECARTUS 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 TECARTUS are at risk for altered or decreased consciousness or coordination in the 8 weeks following TECARTUS 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 TECARTUS. 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 TECARTUS infusion.

Immune

Cytokine release syndrome (CRS)

CRS, including fatal and life-threatening reactions, occurred following treatment with TECARTUS. CRS occurred in 91% (75/82) of patients with MCL, including ≥ Grade 3 (Lee grading system) CRS in 15% of patients. The median time to onset of CRS was 3 days (range: 1 to 13 days) and the median duration of CRS was 10 days (range: 1 to 50 days) for patients with MCL. CRS occurred in 92% (72/78) of patients with ALL, including ≥ Grade 3 (Lee grading system) CRS in 26% of patients. Three patients with ALL had ongoing CRS events at the time of death. The median time to onset of CRS was 4.5 days (range: 1 to 12 days) and the median duration of CRS was 8 days (range: 2 to 63 days) for patients with ALL. The incidence of CRS (first occurrence) within the first seven days after TECARTUS infusion was 90% (70/78) in patients with ALL.

Among all MCL and ALL patients with CRS, key manifestations (>10%) included pyrexia (96%), hypotension (65%), tachycardia (50%), chills (33%), hypoxia (32%), headache (22%), fatigue (17%) and nausea (14%). Serious adverse reactions associated with CRS included hypotension, fever, hypoxia, dyspnea, and tachycardia (see **ADVERSE REACTIONS**).

Ensure that 4 doses of tocilizumab are available for each patient prior to TECARTUS infusion. Monitor patients daily for at least 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 TECARTUS (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. If CRS is suspected, manage 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. 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[c] 8 mg/kg intravenously over 1 hour (not to exceed 800 mg)	N/A

CRS Grade[a]	Tocilizumab	Corticosteroids
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 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, discontinue tocilizumab.	• Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab. • If improving, taper corticosteroids.
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. • If improving, discontinue tocilizumab.	• Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours) until Grade 1, then taper corticosteroids. • If improving, manage as Grade 2. • 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, discontinue tocilizumab.	• Administer methylprednisolone 1000 mg intravenously per day for 3 days. • If improving, taper corticosteroids, and manage as Grade 3. • If not improving, consider alternate immunosuppressants.

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

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

c. Refer to tocilizumab Product Monograph for details.

Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome

Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS), including life-threatening reactions, occurred following treatment with TECARTUS. HLH/MAS occurred in 4% (3/78) of patients with ALL.

Two patients experienced Grade 3 events and 1 patient experienced a Grade 4 event. The median time to onset for HLH/MAS was 8 days (range: 6 to 9 days) with a median duration of 5 days (range: 2 to 8 days). All three patients with HLH/MAS had concurrent CRS symptoms and neurologic events after TECARTUS infusion. Treatment of HLH/MAS should be administered per institutional standards.

Hypogammaglobulinemia

B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with TECARTUS. Hypogammaglobulinemia occurred in 16% of patients with MCL and grade 3 or higher occurred in one patient. B-cell aplasia was observed in 14% and 45% of a subset of patients with MCL who had evaluable blood samples at baseline and at 3 months, respectively. Hypogammaglobulinemia occurred in 9% (7/78) of patients with ALL and no grade 3 or higher events occurred. B-cell aplasia was observed in 89% and 58% of a subset of patients with ALL who had evaluable blood samples at baseline and at 3 months, respectively. Monitor immunoglobulin levels after treatment with TECARTUS 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 TECARTUS. The safety of immunization with live viral vaccines during or following TECARTUS 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 TECARTUS treatment, and until immune recovery following treatment with TECARTUS (see **DRUG INTERACTIONS**).

Hypersensitivity reactions

Serious hypersensitivity reactions including anaphylaxis, may occur due to dimethyl sulfoxide (DMSO) or residual gentamicin in TECARTUS.

Prolonged cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and TECARTUS infusion. In patients with MCL, Grade 3 or higher prolonged cytopenias (still present at Day 30 or with an onset at Day 30 or beyond) following TECARTUS infusion occurred in 57% of patients and included neutropenia (41%), thrombocytopenia (39%), and anemia (18%). In patients with ALL, Grade 3 or higher cytopenias not resolved by Day 30 following TECARTUS infusion occurred in 41% (32/78) of the patients and included neutropenia (28%) and thrombocytopenia (19%). Monitor blood counts after TECARTUS infusion.

Infections

Severe infections, including fatal or life-threatening infections occurred in patients after TECARTUS infusion. Infections occurred in 56% of patients with MCL and 41% (32/78) of patients with ALL. Grade 3 or higher infections occurred in 30% of patients with MCL including bacterial, viral and fungal infections. Grade 3 or higher infections occurred in 27% of patients with ALL including bacterial, viral and fungal infections. Two patients with MCL died due to infection: one patient died due to organizing pneumonia following serious adverse events of Grade 4 respiratory failure and Grade 4 acute respiratory distress syndrome; and one patient died due to staphylococcal bacteremia. Six patients with ALL died due to infection which included: sepsis, fungal pneumonia, unspecified pneumonia, and herpes simplex viraemia. TECARTUS should not be administered to patients with clinically significant active systemic infections. Monitor patients for signs and symptoms of infection before and after TECARTUS infusion and treat appropriately. Administer prophylactic antimicrobials according to local guidelines.

Febrile neutropenia was observed in 6% of patients with MCL and 14% (11/78) of patients with ALL after TECARTUS infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated.

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

Hepatitis B 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, hepatitis C virus (HCV), and human immunodeficiency virus (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 TECARTUS 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 TECARTUS 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, also known as immune effector cell-associated neurotoxicity syndrome (ICANS), have been observed in patients treated with TECARTUS, which could be fatal or life-threatening. Neurologic adverse reactions occurred in 68% (56/82) of patients with MCL, 33% of whom experienced Grade ≥ 3 (severe or life threatening) neurologic adverse reactions. The median time to onset for neurologic adverse reactions was 8 days (range: 1 to 262 days) for patients with MCL with a median duration of 13 days (range: 1 to 567 days). Three patients had ongoing neurologic adverse reactions at the time of death, including one patient with serious encephalopathy and another patient with the reported event of serious confusional state. The remaining unresolved neurologic adverse reactions were Grade 2. Eighty-five percent of all treated patients experienced the first CRS or neurological adverse reaction within the first 7 days after TECARTUS infusion.

Neurologic adverse reactions occurred in 68% (53/78) of patients with ALL, including ≥ Grade 3 neurologic adverse reactions in 32% of patients. The median time to onset for neurologic adverse

reactions was 8 days (range: 1 to 16 days) for patients with ALL with a median duration of 11 days (range: 1 to 75 days). Three subjects had ongoing neurologic adverse reaction at the time of death, including 1 patient each with Grade 3 serious paraparesis, Grade 3 serious paralysis and Grade 4 serious encephalopathy. Ninety-six percent of all treated patients experienced the first CRS or neurologic adverse reaction within the first 7 days after TECARTUS infusion.

Overall, neurologic adverse reactions resolved for 99 out of 109 (91%) patients treated with TECARTUS. Ninety three percent of all MCL and ALL treated patients experienced the first CRS or neurological adverse reaction within the first 7 days after TECARTUS infusion.

The most common treatment-emergent neurologic adverse reactions (>10%) in MCL and ALL patients included tremor (34%), encephalopathy (28%), confusional state (26%), aphasia (21%) and agitation (11%). Serious adverse reactions including encephalopathy, aphasia, confusional state, seizures and ICANS have occurred after treatment with TECARTUS. Monitor patients daily for at least 7 days at the specialized healthcare facility following infusion for signs and symptoms of neurologic adverse reactions.

Monitor patients for signs or symptoms of neurologic adverse reactions/ICANS for 4 weeks after infusion and treat promptly. 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 adverse reaction occur at any time.

Management of neurologic adverse reactions

Monitor patients for signs and symptoms of neurologic adverse reactions/ICANS (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 TECARTUS (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 non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis for any grade neurologic adverse reactions.

Table 3. Neurologic Adverse Reaction/ICANS 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 Dysphasia-not impairing ability to communicate	• Administer tocilizumab per Table 2 for management of Grade 1 CRS.	• Supportive care per institutional standard of care.
	Consider non-sedating, anti-seizure medicines (e.g., 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. • If not improving within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours until the event is Grade 1 or less, then taper corticosteroids. • If improving, discontinue tocilizumab. • If still not improving, manage as Grade 3.	• Administer dexamethasone 10 mg intravenously every 6 hours until the event is Grade 1 or less. • If improving, taper corticosteroids.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 3 Examples include: Somnolence—obtundation or stupor Confusion—severe disorientation Encephalopathy—limiting	• Administer tocilizumab per Grade 2 above. • 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 corticosteroids.	• Administer dexamethasone 10 mg intravenously every 6 hours. • Continue dexamethasone use until the event is Grade 1 or less, then taper corticosteroids. • If not improving, manage as Grade 4.

Grading Assessment[a]	Concurrent CRS	No Concurrent CRS
self-care ADLs Dysphasia—severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly	• If improving, discontinue tocilizumab and manage as Grade 2. • If still not improving, manage as Grade 4.	
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 4 Life-threatening consequences Urgent intervention indicated Requirement for mechanical ventilation Consider cerebral edema	• Administer tocilizumab per Grade 2 above. • 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 improving, then manage as Grade 3. • If not improving, consider alternate immunosuppressants.	• Administer methylprednisolone 1000 mg intravenously per day for 3 days. • If improving, then manage as Grade 3. • If not improving, consider alternate immunosuppressants.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	

Abbreviation: ADLs, activities of daily living.

a. Severity based on Common Terminology Criteria for Adverse Events

b. Refer to tocilizumab Product Monograph for details

Reproductive Health: Female and Male Potential

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

For males and females of reproductive potential who have received TECARTUS, pregnancy and effective methods of contraception 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 TECARTUS.

- **Fertility**

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

7.1 Special Populations

7.1.1 Pregnant Women

There are no available data with TECARTUS use in pregnant women. No animal reproductive and

developmental toxicity studies have been conducted with TECARTUS to assess whether TECARTUS can cause fetal harm when administered to a pregnant woman. It is not known if TECARTUS has the potential to be transferred to the fetus. Based on the mechanism of action of TECARTUS, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia. Therefore, TECARTUS is not recommended for women who are pregnant. Pregnancy after TECARTUS infusion should be discussed with the treating physician.

7.1.2 Breast-feeding

It is unknown if TECARTUS 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 TECARTUS and any potential adverse effects on the breastfed infant from TECARTUS or from the underlying maternal condition.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of TECARTUS in patients less than 18 years of age have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Evidence from clinical studies suggest that efficacy and safety in patients ≥ 65 years of age were consistent with the overall treated patient population. No dose adjustment is required in patients ≥ 65 years of age.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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

- Cytokine Release Syndrome
- Neurologic Adverse Reactions
- Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome
- Hypersensitivity Reactions
- Serious Infections
- Prolonged Cytopenias
- Hypogammaglobulinemia

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, 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 may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Relapsed or Refractory Mantle Cell Lymphoma (MCL)

The safety of TECARTUS was evaluated in a phase 2 single-arm, clinical study (ZUMA-2) in which a total of 82 patients with relapsed/refractory MCL received a single dose of CAR-positive viable T cells (2×10^6 or 0.5×10^6 anti-CD19 CAR T cells/kg) that was weight-based (see **CLINICAL TRIALS**).

The most common non-hematological adverse reactions (in ≥20%) include: pyrexia (94%), CRS (91%), hypotension (57%), encephalopathy (51%), fatigue (50%), tachycardias (45%), other pathogen infections (43%), chills (41%), hypoxia (40%), cough (39%), tremor (38%), musculoskeletal pain (35%), edema (35%), headache (35%), nausea (35%), motor dysfunction (33%), constipation (29%), diarrhea (28%), decreased appetite (26%), dyspnea (26%), rash (22%), insomnia (21%), pleural effusion (21%), aphasia (20%), hypertension (20%), and renal insufficiency (20%).

Serious adverse reactions occurred in 65% of patients. The most common serious adverse reactions (≥ 2%) include: encephalopathy (26%), other pathogen infection (22%), pyrexia (20%), CRS (15%), hypoxia (9%), aphasia (6%), renal insufficiency (6%), pleural effusion (5%), respiratory failure (5%), bacterial infections (4%), dyspnea (4%), fatigue (4%), non-ventricular arrhythmia (4%), viral infections (4%), diarrhea (2%), hypertension (2%), motor dysfunction (2%), seizure (2%), tachycardia (2%), and thrombosis (2%).

Grade 3 or higher adverse reactions were reported in 65% of patients. The most common Grade 3 or higher non-haematological adverse reactions included infections (32%) and encephalopathy (24%). The most common Grade 3 or higher haematological adverse reactions included neutropenia (99%), leukopenia (98%), lymphopenia (96%), thrombocytopenia (65%) and anaemia (56%). Grade 5 (fatal) adverse events were reported in 3 patients and included organizing pneumonia, staphylococcal bacteremia, and cardiac arrest.

In ZUMA-2, 70% of patients received prophylactic allopurinol for TLS and 73% of patients received tocilizumab and/or corticosteroids for the treatment of adverse reactions (including CRS and neurologic adverse reactions), including 51% who required 2 or more doses of tocilizumab.

Table 4 summarizes the adverse reactions that occurred in at least 10% of patients treated with TECARTUS. The median duration of follow-up was 19.2 months.

Table 4 Summary of Adverse Reactions Observed in at Least 10% of Patients Treated with TECARTUS in ZUMA-2

Adverse Reaction	Any Grade n (%) N = 82	Grade 3 or Higher n (%) N= 82
Blood and Lymphatic System Disorders		
Coagulopathy [a]	8 (10)	2 (2)
Cardiac Disorders		
Tachycardias [b]	37 (45)	0
Bradycardias [c]	9 (11)	0
Non-ventricular arrhythmias [d]	8 (10)	3 (4)
Gastrointestinal Disorders		
Nausea	29 (35)	1 (1)
Constipation	24 (29)	0
Diarrhea	23 (28)	4 (5)
Oral pain [e]	14 (17)	0
Abdominal pain [f]	13 (16)	0
Vomiting [g]	11 (13)	0
Dysphagia	8 (10)	2 (2)
General Disorders and Administration Site Conditions		
Pyrexia	77 (94)	13 (16)
Fatigue [h]	41 (50)	1 (1)
Chills	34 (41)	0
Edema [i]	29 (35)	2 (2)
Pain [j]	14 (17)	2 (2)
Immune System Disorders		
Cytokine release syndrome	75 (91)	12 (15)
Hypogammaglobulinemia [k]	13 (16)	1 (1)
Infections and Infestations		
Other pathogen infections	35 (43)	21 (26)
Viral infections	15 (18)	3 (4)
Bacterial infections	11 (13)	5 (6)
Fungal infections	8 (10)	0
Metabolism and Nutrition Disorders		
Decreased appetite	21 (26)	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain [l]	30 (37)	2 (2)
Motor dysfunction [m]	27 (33)	5 (6)
Nervous System Disorders		
Encephalopathy [n]	42 (51)	20 (24)
Tremor	31 (38)	2 (2)
Headache [o]	29 (35)	1 (1)
Aphasia [p]	16 (20)	6 (7)
Dizziness [q]	15 (18)	5 (6)
Neuropathy [r]	11 (13)	2 (2)
Psychiatric Disorders		

Adverse Reaction	Any Grade n (%) N = 82	Grade 3 or Higher n (%) N=82
Insomnia	17 (21)	0
Delirium [s]	15 (18)	4 (5)
Anxiety	14 (17)	0
Renal and Urinary Disorders		
Renal insufficiency [t]	16 (20)	6 (7)
Urine output decreased [u]	9 (11)	1 (1)
Respiratory, Thoracic and Mediastinal Disorders		
Hypoxia	33 (40)	16 (20)
Cough [v]	32 (39)	0
Dyspnea [w]	21 (26)	5 (6)
Pleural effusion	17 (21)	4 (5)
Skin and Subcutaneous Tissue Disorders		
Rash [x]	18 (22)	3 (4)
Vascular Disorders		
Hypotension [y]	47 (57)	23 (28)
Hypertension	16 (20)	9 (11)
Thrombosis [z]	14 (17)	3 (4)

a. Coagulopathy includes coagulopathy, disseminated intravascular coagulation, international normalised ratio increased.
b. Tachycardias includes tachycardia, sinus tachycardia.
c. Bradycardias includes bradycardia, sinus bradycardia.
d. Non-ventricular arrhythmias includes atrial fibrillation, atrial flutter, cardiac flutter, palpitations, supraventricular tachycardia.
e. Oral pain includes oral pain, gingival pain, lip pain, oral mucosal erythema, oropharyngeal pain.
f. Abdominal pain includes abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness.
g. Vomiting includes vomiting, retching.
h. Fatigue includes fatigue, lethargy, malaise.
i. Edema includes eyelid edema, face edema, generalised edema, localised edema, edema, edema peripheral, periorbital edema, peripheral swelling, scrotal edema, swelling face.
j. Pain includes pain, allodynia, dysaesthesia, ear pain, facial pain, non-cardiac chest pain.
k. Hypogammaglobulinemia includes hypogammaglobulinemia, blood immunoglobulin G decreased.
l. Musculoskeletal pain includes musculoskeletal pain, arthralgia, back pain, bone pain, dysarthria, flank pain, groin pain, myalgia, neck pain, pain in extremity.
m. Motor dysfunction includes asthenia, intensive care acquired weakness, mobility decreased, muscle twitching, muscular weakness, myopathy.
n. Encephalopathy includes encephalopathy, altered state of consciousness, amnesia, balance disorder, cognitive disorder, confusional state, disturbance in attention, dysgraphia, dyskinesia, memory impairment, mental status changes, neurotoxicity, somnolence.
o. Headache includes headache, migraine.
p. Aphasia includes aphasia, communication disorder.
q. Dizziness includes dizziness, presyncope, syncope.
r. Neuropathy includes hyperaesthesia, neuropathy peripheral, paraesthesia, paraesthesia oral.
s. Delirium includes delirium, agitation, disorientation, hallucination, hypomania, irritability, nervousness, personality change.
t. Renal insufficiency includes acute kidney injury, blood creatinine increased.
u. Urine output decreased includes urine output decreased, urinary retention.
v. Cough includes cough, upper-airway cough syndrome.

w. Dyspnea includes dyspnea, dyspnea exertional.
x. Rash includes rash, erythema, rash erythematous, rash maculo-papular, rash pustular.
y. Hypotension includes hypotension, orthostatic hypotension.
z. Thrombosis includes thrombosis, deep vein thrombosis, embolism, pulmonary embolism.

Relapsed or Refractory B-Cell Precursor Acute Lymphoblastic Leukemia (ALL)

The safety of TECARTUS was evaluated in a phase 1/2 single-arm, clinical study (ZUMA-3) in which a total of 78 patients with relapsed/refractory ALL received a single dose of CAR-positive viable T cells (1×10^6 anti-CD19 CAR T cells/kg) that was weight-based (see **CLINICAL TRIALS**).

The most common non-hematological adverse reactions (in ≥20%) include: pyrexia (96%), cytokine release syndrome (92%), hypotension (69%), tachycardias (63%), encephalopathy (56%), nausea (41%), chills (40%); headache (38%), fatigue (35%), edema (32%), hypoxia (31%), musculoskeletal pain (31%), motor dysfunction (31%), diarrhea (29%), tremor (29%), abdominal pain (28%), pain (28%), hypomagnesemia (27%), unspecified pathogen infections (24%), aphasia (24%), constipation (24%), rash (23%), decreased appetite (22%), and vomiting (21%).

Serious adverse reactions occurred in 78% of patients. The most common serious adverse reactions (≥2%) were hypotension, cytokine release syndrome, encephalopathy, pyrexia, unspecified pathogen infections, hypoxia, bacterial infections, tachycardias, aphasia, respiratory failure, febrile neutropenia, seizure, motor dysfunction, dyspnea, edema, fungal infections, musculoskeletal pain, viral infections, coagulopathy, delirium, fatigue, and hemophagocytic lymphohistiocytosis.

Grade 3 or higher adverse reactions were reported in 90% of patients. The most common Grade 3 or higher non-haematological adverse reactions included hypophosphatemia (47%), pyrexia (38%), hypotension (36%), alanine aminotransferase increased (31%), CRS (26%), aspartate aminotransferase increased (23%), hypoxia (23%), hyperglycemia (22%), encephalopathy (21%), hypoxia (22%), hypocalcemia (22%), blood uric acid increased (21%), direct bilirubin increased (19%), hyponatremia (19%), unspecified pathogen infections (18%), hypokalemia (13%), aphasia (14%), and bilirubin increased (10%). The most common Grade 3 or higher haematological adverse reactions was febrile neutropenia (14%).

In ZUMA-3, 50% of patients received prophylactic allopurinol for TLS and 86% of patients received tocilizumab and/or corticosteroids for the treatment of adverse reactions (including CRS and neurologic adverse reactions), including 62% who required 2 or more doses of tocilizumab.

Fatal adverse reactions occurred in 6% (5/78) of patients including GvHD, cerebral edema, sepsis, and fungal pneumonia. Of the 5 patients who had fatal adverse reactions: one patient with fatal pneumonia had pre-existing pneumonia prior to study enrollment, and one patient with fatal sepsis had prolonged cytopenia and immunosuppression from prior therapies and underlying disease.

Table 5 summarizes the adverse reactions that occurred in at least 10% of patients treated with TECARTUS. The median duration of follow-up was 20.0 months.

Table 5: Summary of Adverse Reactions Observed in at Least 10% of Patients Treated with TECARTUS in ZUMA-3

ADR	Any Grade N = 78 n (%)	≥ Grade 3 N = 78 n (%)
Blood and lymphatic system disorders		
Coagulopathy[a]	13 (17)	4 (5)
Febrile Neutropenia	11 (14)	11 (14)
Cardiac disorders		
Tachycardias[b]	49 (63)	5 (6)
Bradycardias[c]	10 (13)	1 (1)
Gastrointestinal disorders		
Nausea	32 (41)	1 (1)
Diarrhea	23 (29)	3 (4)
Abdominal pain[d]	22 (28)	0 (0)
Constipation	19 (24)	0 (0)
Vomiting	16 (21)	2 (3)
General disorders and administration site conditions		
Pyrexia	75 (96)	30 (38)
Chills	31 (40)	0 (0)
Edema[e]	25 (32)	5 (6)
Fatigue[f]	27 (35)	1 (1)
Pain[g]	22 (28)	1 (1)
Immune system disorders		
Cytokine release syndrome	72 (92)	20 (26)
Infections and infestations		
Unspecified pathogen infections[h]	19 (24)	14 (18)
Bacterial infections[i]	12 (15)	6 (8)
Fungal infections[j]	10 (13)	4 (5)
Metabolism and nutrition disorders		
Hypomagnesemia[k]	21 (27)	0 (0)
Decreased appetite	17 (22)	1 (1)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[l]	24 (31)	5 (6)
Motor dysfunction[m]	24 (31)	4 (5)

Nervous system disorders		
Encephalopathy[n]	44 (56)	16 (21)
Headache	30 (38)	1 (1)
Tremor	23 (29)	1 (1)
Aphasia	19 (24)	11 (14)
Dizziness[o]	10 (13)	1 (1)
Psychiatric disorders		
Delirium[p]	14 (18)	4 (5)
Anxiety[q]	11 (14)	2 (3)
Insomnia	10 (13)	0 (0)
Respiratory, thoracic and mediastinal disorders		
Hypoxia	24 (31)	18 (23)
Respiratory failure[r]	12 (15)	7 (9)
Cough[s]	9 (12)	0 (0)
Dyspnea	9 (12)	1 (1)
Skin and subcutaneous tissue disorders		
Rash[t]	18 (23)	0 (0)
Skin Disorder[u]	13 (17)	1 (1)
Vascular disorders		
Hypotension[v]	54 (69)	28 (36)
Hemorrhage[w]	11 (14)	3 (4)
Hypertension	10 (13)	5 (6)

a. Coagulopathy includes blood fibrinogen decreased, coagulopathy, disseminated intravascular coagulation, hypofibrinogenemia, international normalized ratio increased
b. Bradycardias includes bradycardia, sinus bradycardia
c. Tachycardias includes sinus tachycardia, tachycardia, ventricular tachycardia
d. Abdominal pain includes abdominal discomfort, abdominal distension, abdominal pain, abdominal pain upper, dyspepsia
e. Edema includes ascites, face edema, fluid overload, generalized edema, gravitational edema, lymphedema, edema, edema peripheral, peripheral swelling, swelling face, tongue edema
f. Fatigue includes fatigue, lethargy, malaise
g. Pain includes chest discomfort, ear pain, eye pain, lymph node pain, musculoskeletal chest pain, non-cardiac chest pain, pain, paranasal sinus discomfort, pelvic pain, procedural pain, proctalgia, sinus pain, urinary tract pain
h. Unspecified pathogen infections include device related infection, infection, nasopharyngitis, pneumonia, sepsis, sinusitis, skin infection, upper respiratory tract infection, urinary tract infection
i. Bacterial infections includes bacteremia, bacterial disease carrier, catheter bacteremia, cellulitis, cellulitis of male external genital organ, clostridial infection, clostridium difficile colitis, clostridium difficile infection, enterococcal bacteremia, escherichia bacteremia, escherichia infection, escherichia sepsis, pseudomonas infection, staphylococcal bacteremia, staphylococcal infection, wound infection staphylococcal
j. Fungal infections include candida infection, fungal skin infection, fungal test positive, oral candidiasis, osteomyelitis fungal, pneumocystis jirovecii pneumonia, pneumonia fungal, sinusitis fungal
k. Hypomagnesemia includes hypomagnesemia, magnesium deficiency
l. Musculoskeletal pain includes arthralgia, back pain, bone pain, coccydynia, dysarthria, flank pain, musculoskeletal pain, myalgia, neck pain, pain in extremity
m. Motor dysfunction includes asthenia, intensive care unit acquired weakness, monoplegia, muscle spasms, muscular weakness, musculoskeletal stiffness, myoclonus, paraparesis
n. Encephalopathy includes altered state of consciousness, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, dysgraphia, encephalopathy, immune effector cell-associated neurotoxicity

syndrome, memory impairment, mental status changes, slow response to stimuli, slow speech, somnolence, speech disorder

o. Dizziness includes dizziness, syncope
p. Delirium includes agitation, delirium, delusion, disorientation, hallucination
q. Anxiety includes anxiety, restlessness
r. Respiratory failure includes acute respiratory distress syndrome, acute respiratory failure, bradypnea, respiratory distress, respiratory failure, tachypnea
s. Cough includes cough, productive cough
t. Rash includes dermatitis bullous, drug eruption, rash, rash macular, rash maculo-popular, rash pustular, toxic skin eruption, urticaria
u. Skin disorder includes alopecia, decubitus ulcer, dry skin, hyperhidrosis, pruritus, skin hyperpigmentation, skin lesion, skin ulcer
v. Hypotension includes distributive shock, hypotension, orthostatic hypotension, septic shock, shock
w. Hemorrhage includes conjunctival hemorrhage, contusion, diarrhea hemorrhagic, epistaxis, gastric hemorrhage, hematochezia, hematoma, hematoma muscle, hematuria, lower gastrointestinal hemorrhage, petechia, pulmonary alveolar hemorrhage, rectal hemorrhage, retinal hemorrhage, vaginal hemorrhage, vitreous hemorrhage

8.3 Less Common Clinical Trial Adverse Reactions

Other clinically important adverse reactions (any grade) that occurred in less than 10% of patients treated with TECARTUS include the following:

Relapsed or Refractory Mantle Cell Lymphoma (MCL)

- *Gastrointestinal disorders:* dry mouth (7%)
- *Metabolism and nutrition disorders:* dehydration (6%)
- *Nervous system disorders:* ataxia (7%), seizure (5%), increased intracranial pressure (2%)
- *Respiratory, thoracic and mediastinal disorders:* respiratory failure (6%), pulmonary edema (4%)
- *Vascular disorders:* hemorrhage (7%)

Relapsed or Refractory B-Cell Precursor Acute Lymphoblastic Leukemia (ALL)

- *Cardiac disorders:* cardiac failure (4%), non-ventricular arrythmias (6%)
- *Eye disorders:* visual impairment (9%)
- *Gastrointestinal disorders:* oral pain (9%), dry mouth (6%), dysphagia (4%)
- *Immune system disorders:* hypogammaglobulinemia (9%), hypersensitivity (3%), hemophagocytic lymphohistiocytosis (4%), graft-versus host disease (6%)
- *Infections and Infestations:* viral infections (6%)
- *Metabolism and nutrition disorders:* dehydration (3%), tumor lysis syndrome (1%)
- *Nervous system disorders:* seizure (8%), neuropathy (4%), ataxia (5%), paraparesis (3%), increased intracranial pressure (1%), brain herniation (1%), cauda equina syndrome (1%),
- monoplegia (1%)
- *Renal and urinary disorders:* renal insufficiency (6%), urine output decreased (6%)
- *Respiratory, thoracic and mediastinal disorders:* pulmonary edema (6%), pleural effusion (4%), pneumonitis (4%)

- *Vascular disorders:* thrombosis (3%)

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

Clinical Trial Findings

Table 6 describes the laboratory abnormalities of Grade 3 or 4 that occurred in at least 10% of patients in ZUMA-2.

Table 6 Grade 3 or 4 Laboratory Abnormalities in ≥ 10% of Patients in ZUMA-2 Following TECARTUS Infusion (N = 82)

	Grades 3 or 4 n (%)
Neutropenia	81 (99)
Leukopenia	80 (98)
Lymphopenia	79 (96)
Thrombocytopenia	53 (65)
Anemia	46 (56)
Hypophosphatemia	25 (30)
Hypocalcemia	17 (21)
Blood uric acid increased	14 (17)
Hyponatremia	13 (16)
Aspartate Aminotransferase increased	12 (15)
Alanine Aminotransferase increased	12 (15)
Hypokalemia	8 (10)

Table 7 describes the laboratory abnormalities of Grade 3 or 4 that occurred in at least 10% of patients in ZUMA-3.

Table 7 Grade 3 or 4 Laboratory Abnormalities in ≥ 10% of Patients in ZUMA-3 Following TECARTUS Infusion (N = 78)

	Grades 3 or 4 n (%)
Leukopenia	77 (99)
Neutropenia	76 (97)
Lymphopenia	75 (96)
Thrombocytopenia	68 (87)
Anemia	60 (77)
Hypophosphatemia	37 (47)
Alanine aminotransferase increased	24 (31)
Aspartate aminotransferase increased	18 (23)
Hyperglycemia	17 (22)
Hypocalcemia	17 (22)
Blood uric acid increased	16 (21))
Direct bilirubin increase	15 (19)
Hyponatremia	15 (19)
Hypokalemia	10 (13)
Bilirubin increased	8 (10)

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No formal interaction studies have been performed with TECARTUS.

9.4 Drug-Drug Interactions

Pharmacokinetic Interactions

No pharmacokinetic drug interaction studies have been performed with TECARTUS.
Prophylactic use of systemic corticosteroids may interfere with the activity of TECARTUS. Prophylactic use of systemic corticosteroids is not recommended before infusion of TECARTUS.

Among patients with MCL, administration of corticosteroids as per the CRS/neurologic adverse event treatment algorithm does not impact the expansion and persistence of CAR T cells. Among patients with ALL, there is not sufficient information to draw a conclusion on the impact of corticosteroids or tocilizumab on the expansion and persistence of CAR T cells.

Pharmacodynamic Interactions

The immunization with vaccines during or following TECARTUS 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 TECARTUS; vaccination with live viral vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during TECARTUS treatment, and until immune recovery following treatment with TECARTUS.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

TECARTUS, 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.

10.2 Pharmacodynamics

After TECARTUS 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 generally observed within 8 days after infusion and levels generally returned to baseline within 28 days.

Due to the on-target effect of TECARTUS, TECARTUS treatment can result in a period of B-cell aplasia and hypogammaglobulinemia.

10.3 Pharmacokinetics

Following infusion (target dose of 2×10^6 anti-CD19 CAR T cells/kg) of TECARTUS in ZUMA-2, 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 to 15 days after TECARTUS infusion. The number of anti-CD19 CAR T cells in blood was associated with objective response [complete remission (CR) or partial remission (PR)].

Following infusion of a target dose of 1×10^6 anti-CD19 CAR T cells/kg of TECARTUS in ZUMA-3 (phase 2), anti-CD19 CAR T cells exhibited an initial rapid expansion followed by a decline to near baseline levels by 6 months. Median time to peak levels of anti-CD19 CAR T cells was within the first 15 days after TECARTUS infusion.

Table 8 and Table 9 provides the cellular kinetic parameters observed in ZUMA-2 and ZUMA-3, respectively.

Table 8 Cellular Kinetic parameters of TECARTUS in adult patients with relapsed or refractory Mantle Cell Lymphoma

Parameter n, Median (Min, Max)	Responding Patients N = 63	Non-Responding Patients N = 5
Peak (cells/µL)	n=62, 97.52 (0.24, 2589.47)	n=5, 0.39 (0.16, 22.02)
T_{max} (day)	15 (8, 31)	15 (8, 16)
Median $AUC_{0\text{-}28d}$ (days x cells/ µL)	n=62, 1386.28 (3.83, 2.77 x 10^4)	n=5, 5.51 (1.81, 293.86)

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 2014.
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.
Time-to-peak is defined as number of days from TECARTUS infusion to the date when the CAR T cells in blood firstly reached the maximum post-baseline level.

Table 9 Cellular Kinetic parameters of TECARTUS in adult patients with Relapsed or Refractory B-Cell Precursor Acute Lymphoblastic Leukemia

Parameter n, Median (Min, Max)	Responding Patients N = 32	Non-Responding Patients N = 17
Peak (cells/µL)	n=32 38.35 (1.31, 1533.40)	n= 17 0.49 (0, 183.50)
T_{max} (day)	15 (8, 30)	13 (7, 32)
Median AUC_{0-28d} (days x cells/ µL)	n=32 424.03 (14.12, 19390.42)	n= 17 7.9 (0, 889.0)

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 2014.
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.
Time-to-peak is defined as number of days from TECARTUS infusion to the date when the CAR T cells in blood firstly reached the maximum post-baseline level.

Among patients with MCL, Median peak anti-CD19 CAR T-cell values were 74.08 cells/µL in patients ≥ 65 years of age (n = 39) and 112.45 cells/µL in patients < 65 years of age (n = 28). Median anti-CD19 CAR T-cell AUC values were 876.48 cells/µL·day in patients ≥ 65 years of age and 1640.21 cells/µL·day in patients < 65 years of age.

Among patients with ALL, median peak anti-CD19 CAR T-cell levels were 34.8 cells/µL in evaluable patients ≥ 65 years of age (n=7) and 17.4 cells/µL in evaluable patients < 65 years of age (n = 43). Median anti-CD19 CAR T-cell AUC Day 0-28 values were 425.0 cells/µL·day in patients ≥ 65 years of age and 137.7cells/µL·day in patients < 65 years of age..

Gender had no significant impact on $AUC_{Day\ 0-28}$ and C_{max} of TECARTUS.

Hepatic and renal impairment studies of TECARTUS were not conducted.

11 STORAGE, STABILITY AND DISPOSAL

Storage

- TECARTUS must be stored in the VAPOR 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 1 year when stored frozen in the vapor 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.

12 SPECIAL HANDLING INSTRUCTIONS

TECARTUS 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 TECARTUS.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: brexucabtagene autoleucel

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

Product Characteristics

TECARTUS (brexucabtagene autoleucel suspension for intravenous infusion) is a CD19-directed genetically modified autologous T cell immunotherapy. To prepare TECARTUS, 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.

TECARTUS 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 and anti-CD28 antibodies 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 manufacture of TECARTUS includes a T-cell enrichment step that may reduce the likelihood of circulating CD19 expressing tumor cells in patients' leukapheresis material driving the activation, expansion, and exhaustion of the anti CD19 CAR T cells during the ex vivo manufacturing process. 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, STORAGE, STABILITY AND DISPOSAL, SPECIAL HANDLING INSTRUCTIONS**).

In addition to T cells, TECARTUS may contain NK cells. The formulation contains CryoStor, sodium chloride (NaCl) and Human Serum Albumin (HSA).

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Relapsed or Refractory Mantle Cell Lymphoma

Table 10 Summary of Patient Demographics for the Clinical Trial in Relapsed or Refractory MCL

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex n (%)
ZUMA-2	Phase 2, single-arm, open-label, multicentre trial in adult patients with relapsed or refractory mantle cell lymphoma	Single intravenous infusion of TECARTUS at a target dose of 2×10^6 CAR-positive viable T cells/kg (maximum permitted dose: 2×10^8 CAR-positive viable T cells)	74 patients were leukapheresed; 69 patients treated with conditioning chemotherapy; 68 patients received TECARTUS	Leukapheresed and Treated groups: 65 years (range: 38 to 79 years)	Leukapheresed: 62 (84%) males 12 (16%) females Treated: 57 (84%) males 11 (16%) females

ZUMA-2 is a phase 2 single-arm, open-label, multicentre trial that evaluated the efficacy and safety of a single infusion of TECARTUS in adult patients with relapsed or refractory mantle cell lymphoma (MCL) who had previously received anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a Bruton's tyrosine kinase (BTK) inhibitor (ibrutinib or acalabrutinib). Eligible patients also had disease progression after their last regimen or refractory disease to their most recent therapy. The study excluded patients with active or serious infections, prior allogeneic hematopoietic stem cell transplantation (HSCT), detectable cerebrospinal fluid malignant cells or brain metastases, and any history of central nervous system lymphoma or CNS disorders.

Seventy-four patients were leukapheresed and 68 patients received a single infusion of TECARTUS. Three patients did not receive TECARTUS due to manufacturing failure. Two patients did not receive TECARTUS due to progressive disease (death) following leukapheresis. One patient who received lymphodepleting chemotherapy was not treated with TECARTUS due to ongoing active atrial fibrillation. Among the 68 patients who received TECARTUS, the median time from leukapheresis to product delivery was 16 days (range: 11 to 42 days, with the exception of one outlier of 128 days), and the median time from leukapheresis to TECARTUS infusion was 27 days (range: 19 to 74 days, with the exception of one outlier of 134 days).

Among the 68 patients who received TECARTUS, 61 (90%) received the target dose of 2×10^6 anti-CD19 CAR-positive viable T cells/kg. The remaining 7 patients received doses of 0.6, 1.0, 1.6, 1.8, 1.8, 1.9 and 1.9×10^6 anti-CD19 CAR-positive viable T cells/kg. All treated patients received TECARTUS infusion on Day 0 and were hospitalized until at least Day 7. 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 TECARTUS. Bridging therapy between leukapheresis and lymphodepleting chemotherapy was permitted to control disease burden.

Of the 68 patients treated with TECARTUS, the median age was 65 years (range: 38 to 79 years), 84% were male, and 91% were white. Most (85%) had stage IV disease and 54% had bone marrow involvement. The median number of prior therapies was 3 (range: 1 to 5); 43% of patients relapsed after autologous HSCT, while the remaining either relapsed after (18%) or were refractory to (40%) their last therapy for MCL. Twenty-five percent of patients had blastoid MCL. Twenty-five (37%) patients received bridging therapy following leukapheresis and prior to administration of TECARTUS: 19 (28%) patients were treated with a BTK inhibitor, 11 (16%) with a corticosteroid, and 6 (9%) with both a BTK inhibitor and a corticosteroid.

The primary endpoint was objective response rate (ORR) as determined by Lugano 2014 criteria by an independent review committee (Table 11).

Study Results

An inferential analysis set (IAS) was defined a priori which consisted of the first 60 patients treated with TECARTUS who were evaluated for response 6 months after the Week 4 disease assessment after TECARTUS infusion. In this analysis set of 60 patients, the ORR was 93% with a CR rate of 67%. Efficacy results for the modified intent to treat (mITT) population (N=68), including all patients treated with TECARTUS, are shown in Table 11.

Table 11 Summary of Efficacy Results in Adult Patients with Relapsed or Refractory MCL

	All treated patients (mITT) N=68
Response Rate	
Objective Response Rate[a], n (%) [95% CI]	62 (91%) [81.8, 96.7]
Complete Remission Rate, n (%) [95% CI]	44 (65%) [52.2, 75.9]
Partial Remission Rate, n (%) [95% CI]	18 (26%) [16.5, 38.6]
Duration of Response (DOR)[b]	
Median in months [95% CI] Range[c] in months	NR [10.4, NE] 0.0+, 35.0+
DOR, if best response is CR, median in months [95% CI] Range[c] in months	NR [14.4, NE] 1.6+, 35.0+
DOR, if best response is PR, median in months [95% CI] Range[c] in months	2.2 [1.4, 4.9] 0.0+, 28.2
Median Follow-up for DOR in Months [95% CI]	13.8 [11.3, 20.5]

CI, confidence interval; CR, complete remission; NE, not estimable; NR, not reached; PR, partial remission.

a. Per the International Working Group Lugano Classification (Cheson 2014), as assessed by the Independent Radiology Review Committee.
b. Among all responders. DOR is measured from the date of first objective response to the date of progression or death.
c. A + sign indicates a censored value.

The median time to response was 1 month (range: 0.8 to 3.1 months). The DOR was longer in patients who achieved CR, as compared to patients with a best response of partial remission (PR). Of the 44 patients who achieved CR, 2 had stable disease and 22 had PR at their initial tumor assessment and converted to CR with a median time to conversion of 2.3 months (range: 1.8 to 8.1 months).

Relapsed or Refractory B-Cell Precursor Acute Lymphoblastic Leukemia

Table 12 Summary of Patient Demographics for the Clinical Trial in Relapsed or Refractory B-Cell Precursor ALL (Phase 2)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex n (%)
ZUMA-3	Phase 2, open-label, single-arm, multicenter trial in adult patients with relapsed or refractory b-cell precursor acute lymphoblastic leukemia	Single intravenous infusion of TECARTUS at a target dose of 1×10^6 CAR-positive viable T cells/kg (maximum permitted dose: 1×10^8 CAR-positive viable T cells)	71 patients were leukapheresed; 57 patients treated with conditioning chemotherapy; 55 patients received TECARTUS	Leukapheresed and Treated groups (median): 40 years (range: 19 to 84 years)	Leukapheresed: 41 (58%) males 30 (42%) females Treated: 33 (60%) males 22 (40%) females

ZUMA-3 is a Phase 1/2 open-label, single-arm, multicenter trial that evaluated the efficacy and safety of TECARTUS in adult patients with B-precursor ALL. Relapsed or refractory was defined as one of the following: primary refractory; first relapse following a remission lasting ≤ 12 months; relapsed or refractory after second-line or higher therapy; relapsed or refractory after allogeneic stem cell transplant (allo-SCT) (provided the transplant occurred ≥ 100 days prior to enrollment and that no immunosuppressive medications were taken ≤ 4 weeks prior to enrollment). The study excluded patients with active or serious infections, active graft-vs-host disease, any history of CNS disorders including CNS-2 disease with neurologic changes and CNS-3 disease irrespective of neurological changes, ECOG status ≥ 2, and a history of grade 4 neurologic events or grade 4 CRS with prior CD19-directed therapy.

Following lymphodepleting chemotherapy, TECARTUS was administered to patients as a single intravenous infusion at a target dose of 1×10^6 anti-CD19 CAR T cells/kg (maximum permitted dose: 1×10^8 cells). The lymphodepleting regimen consisted of fludarabine 25 mg/m^2 intravenously over 30 minutes on the 4th, 3rd, and 2nd day and cyclophosphamide 900 mg/m^2 over 60 minutes on the 2nd day before TECARTUS. Of the 55 patients who received TECARTUS, 51 patients received bridging therapy between leukapheresis and lymphodepleting chemotherapy to control disease burden. One patient who responded to bridging chemotherapy prior to TECARTUS infusion was excluded from the efficacy analysis based on the mITT.

Of the 54 patients who were efficacy evaluable, the median age was 40 years (range: 19 to 84 years), 61% were male, and 67% were white. At enrollment, 46% had refractory relapse, 26% had primary refractory disease, 20% had untreated second or later relapse, and 7% had first untreated relapse. Patients had a median of 2 prior lines of therapy (range: 1 to 8 prior lines). Among prior therapies, 43% of patients were previously treated with allo-SCT, 46% with blinatumomab, and 22% with inotuzumab. Twenty-six percent of patients were Philadelphia chromosome (Ph$^+$). Of the 71 patients included in the full analysis set (FAS; enrolled and leukapheresed), the median age was 44 years (range: 19 to 84 years), 58% were male, and 72% were white. At enrollment, 46% had refractory relapse, 24% had primary

refractory disease, 21% had untreated second or later relapse, and 8% had first untreated relapse. Among prior therapies, 39% of patients were previously treated with allo-SCT, 18% with blinatumomab, and 23% with inotuzumab. Twenty-seven percent of patients were Philadelphia chromosome (Ph^+).

Seventy-one patients were leukapheresed. Six patients did not receive TECARTUS due to manufacturing failure. Eight other patients were not treated, primarily due to AEs or not meeting eligibility criteria following leukapheresis. Two patients who underwent leukapheresis and received lymphodepleting chemotherapy were not treated with TECARTUS; one patient experienced bacteremia and neutropenic fever and the other patient did not meet eligibility criteria after lymphodepleting chemotherapy. The median time from leukapheresis to product delivery was 16 days (range: 11 to 42 days) and the median time from leukapheresis to TECARTUS infusion was 29 days (range: 20 to 60 days). All treated patients received TECARTUS infusion on Day 0 and were hospitalized until Day 7 at the minimum. Among the 55 patients who received TECARTUS, 54 (98%) received within 10% of the planned dose (for patients weighing $\leq$ 100 kg: target dose of 1.0×10^6 anti-CD19 CAR-positive viable T cells/kg; for patients weighing >100 kg: target flat dose of 1×10^8 anti-CD19 CAR T cells). One subject who weighed > 100 kg received a flat dose of 0.81×10^8 anti-CD19 CAR T cells.

The primary endpoint was overall complete remission rate (OCR=complete remission [CR] + complete remission with incomplete hematologic recovery [CRi]) in patients treated with TECARTUS as determined by an independent review.

Study Results

At the time of the primary analysis, efficacy evaluable patients were followed for at least 10 months with a median follow-up time of 12.3 months.

Based on the data cut-off date for the primary analysis, the OCR rate was 64.8% with a CR rate of 53.7% in the mITT analysis set. The efficacy results are presented in Table 13.

Table 13. Summary of Efficacy Results in Adult Patients with Relapsed or Refractory B-Cell Precursor ALL (Phase 2)

	mITT[a] N = 54	FAS N = 71
OCR rate (CR + CRi) n (%) [95% CI]	35 (64.8) [51.0, 77.0]	36 (50.7) [39, 63]
CR rate, n (%) [95% CI]	29 (53.7) [40.0, 67.0]	30 (42.3) [31, 55]
Duration of Remission, median in months [95% CI] Median range in months	13.6 [9.4, NE] (0.03+, 16.07+)	13.6 [8.7, NE] (0.03+, 16.07+)

CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete blood count recovery; NE, not estimable; OCR, overall complete remission

a. Of the 71 patients that were enrolled (and leukapheresed), 57 patients received conditioning chemotherapy, and 55 patients received TECARTUS. 54 patients were included in the efficacy evaluable population (modified intention to treat, mITT).
b. The + sign denotes a censored value

Among the 29 patients who achieved a CR in the mITT analysis, the median DOR was not reached [95% CI: 9.6, NE]. Among the 6 patients with CRi in the mITT analysis, the median DOR was 6.9 months [95% CI: 1.0, NE]. The median time to CR was 57 days (range: 26 to 178 days).

In the 21-month follow-up analysis of ZUMA-3 Phase 2 (independent review; mITT population), the OCR rate was consistent with the primary analysis. The median DOR was 18.6 months (95% CI: 9.4, Not Evaluable) with a median follow-up time for DOR of 16.9 months.

14.3 Immunogenicity

TECARTUS 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. To date, no confirmed anti-CAR T-cell antibody immunogenicity has been observed in ZUMA-2. Based on an initial screening assay in ZUMA-2, 17 patients tested positive for antibodies; however, a confirmation orthogonal cell-based assay demonstrated that all 17 patients were antibody negative at all time points tested. Based on an initial screening assay in ZUMA-3, 16 of 100 patients tested positive for antibodies at any timepoint. Among patients with evaluable samples for confirmatory testing, two patients were confirmed to be antibody-positive after treatment. One of the two patients had a confirmed positive antibody result at Month 6. The second patient had a confirmed antibody result at retreatment Day 28 and Month 3. There is no evidence that the kinetics of initial expansion and persistence of TECARTUS, or the safety or effectiveness of TECARTUS, was altered in these patients.

15 MICROBIOLOGY

Not applicable.

16 NON-CLINICAL TOXICOLOGY

TECARTUS 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 TECARTUS. No studies have been conducted to evaluate the effects of TECARTUS on fertility.

17 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

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
TECARTUS™
(brexucabtagene autoleucel)
Suspension for Intravenous Infusion

*Read this carefully before you start taking **Tecartus** (pronounced* tek-ahr-tuhs*). 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 **Tecartus**.*

Serious Warnings and Precautions

Tecartus 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 **Tecartus** 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 **Tecartus** by an experienced healthcare professional at specialized treatment centres.

What is Tecartus used for?

- **Tecartus** is a treatment for your mantle cell lymphoma (MCL) and acute lymphoblastic leukemia (ALL) – two forms of white blood cell cancer.
- For MCL, it is used when at least two other available medicines have stopped working for you.
- For ALL, it is used when at least one other available medicine has stopped working for you.

How does Tecartus work?

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

What are the ingredients in Tecartus?

- Medicinal ingredients: brexucabtagene autoleucel
- Non-medicinal ingredients: Cryostor®, sodium chloride, human serum albumin

Tecartus comes in the following dosage forms:

Tecartus 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 Tecartus if:

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

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Tecartus. 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 and any related side effects from the transplant such as graft versus host disease (GVHD), 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 **Tecartus** 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 **Tecartus** because the treatment can cause sleepiness, confusion, weakness, memory and coordination problems.
- Do not donate blood, organs, tissues and cells for transplantation after **Tecartus** treatment.

- Cases of progressive multifocal leukoencephalopathy (PML) have been reported following use of other CAR T products. 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, 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 Tecartus:

- Corticosteroids use prior to **Tecartus** infusion may make **Tecartus** less effective.
- Vaccines: **Tecartus** may make some vaccines less effective. It may not be safe for you to receive live viral vaccine (a type of vaccine made from weakened virus) during or shortly after **Tecartus**.

How will I receive Tecartus:

- Since **Tecartus** 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 centre to make your **Tecartus**.
- Before you get **Tecartus**, you will get 3 days of chemotherapy to prepare your body.
- When your **Tecartus** 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 **Tecartus** 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 **Tecartus**. 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.
- You will be asked to enrol in a registry, maintained by the Center for International Blood and Marrow Transplant Research (CIBMTR), in order to better understand the long-term effects of **Tecartus**. Additional information can be obtained from: contactus@cibmtr.org.

Usual dose:

Tecartus 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) for MCL and 1×10^6 anti-CD19 CAR-positive viable T cells per kg body weight, with a maximum of 1×10^8 CAR-positive viable T cells (if you weigh 100 kg or higher) for ALL. The entire content of the bag should be given to you as a single, one-time treatment.

What are possible side effects from using Tecartus?

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

Very common:

- Fever, chills, 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
- Changes in rate of the heartbeat
- Decreased appetite, sore mouth
- Difficulty sleeping, anxiety
- Swelling
- Rash
- Infections caused by fungi and bacteria
- Blurred vision
- Excessive bleeding
- Changes to the color of the skin

Common:

- Dry mouth, dehydration
- Loss of control of body movements
- Increase of the pressure inside your skull

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)		✓	
Spontaneous or prolonged and excessive bleeding (coagulopathy)		✓	✓
Very little or no urine (possible symptoms of acute kidney injury)		✓	
Blood clots that lower blood flow (thrombosis)		✓	
Changes in functioning or rhythm of the heart (tachycardias, bradycardias, non-ventricular arrythmias)		✓	
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)		✓	
State of severe confusion (delirium)		✓	✓
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)		✓	
Reduced levels of calcium in the blood, possible leading to muscle spasms, numbness of the hands, feet, or lips (hypocalcemia)		✓	
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)		✓	
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)		✓	✓
Difficulty to swallow (dysphagia)		✓	✓
A syndrome of pathologic immune activation characterized by clinical signs and symptoms of extreme inflammation such as fever, malaise,		✓	✓

yellow color of your skin and eyes (hemophagocytic lymphohistiocytosis/macrophage activation syndrome [HLH/MAS])			
Breathlessness, difficulty breathing when lying down (possible symptoms of heart failure)		✓	✓
RARE			
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])		✓	✓
Producing less urine than normal and/or muscle spasms, possible symptom of an increase in potassium, phosphate and uric acid in the blood that can cause kidney problems (possible symptom of tumor lysis syndrome)		✓	✓
Severe headache, weakness, loss of consciousness (possible brain herniation)		✓	✓

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 Tecartus:

- 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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.gilead.ca, or by calling 1-866-207-4267.

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