1. NAME OF THE MEDICINAL PRODUCT

Tecartus 0.4 – 2 × 10^8 cells dispersion for intravenous infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Tecartus (brexucabtagene autoleucel) is a genetically modified autologous cell-based product containing T cells transduced *ex vivo* using a retroviral vector expressing an anti-CD19 chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment (scFv) linked to CD28 co-stimulatory domain and CD3-zeta signalling domain.

2.2 Qualitative and quantitative composition

Mantle cell lymphoma

Each patient-specific infusion bag of Tecartus contains brexucabtagene autoleucel at a batch-dependent concentration of autologous T cells genetically modified to express an anti-CD19 chimeric antigen receptor (CAR-positive viable T cells). The medicinal product is packaged in one infusion bag overall containing a cell dispersion for infusion of a target dose of 2 × 10^6 anti-CD19 CAR-positive viable T cells/kg body weight (range: 1 × 10^6 – 2 × 10^6 cells/kg), with a maximum of 2 × 10^8 anti-CD19 CAR-positive viable T cells suspended in a Cryostor CS10 solution.

Each infusion bag contains approximately 68 mL of dispersion for infusion.

Acute lymphoblastic leukaemia

Each patient-specific infusion bag of Tecartus contains brexucabtagene autoleucel at a batch-dependent concentration of autologous T cells genetically modified to express an anti CD19 chimeric antigen receptor (CAR-positive viable T cells). The medicinal product is packaged in one infusion bag overall containing a cell dispersion for infusion of a target dose of 1 × 10^6 anti CD19 CAR positive viable T cells/kg body weight, with a maximum of 1 × 10^8 anti CD19 CAR positive viable T cells suspended in a Cryostor CS10 solution.

Each infusion bag contains approximately 68 mL of dispersion for infusion.

Excipient(s) with known effect

This medicinal product contains 300 mg sodium.
Each dose contains 0.05 mL of dimethyl sulfoxide (DMSO) per mL of Tecartus.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for intravenous infusion.

A clear to opaque, white to red suspension of cells.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mantle cell lymphoma

Tecartus is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor unless ineligible to BTK inhibitor.

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

Acute lymphoblastic leukaemia

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

4.2 Posology and method of administration

Tecartus must be administered in a qualified treatment centre by a physician with experience in the treatment of haematological malignancies and trained for administration and management of patients treated with Tecartus. At least 1 dose of tocilizumab for use in the event of cytokine release syndrome (CRS) and emergency equipment must be available prior to infusion. The qualified treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose.

Posology

Tecartus is intended for autologous use only (see section 4.4).

Mantle cell lymphoma
Treatment consists of a single dose for infusion containing a dispersion for infusion of CAR-positive viable T cells in one container. The target dose is 2×10^6 CAR-positive viable T cells per kg of body weight (range: $1 \times 10^6 – 2 \times 10^6$ cells/kg), or maximum of 2×10^8 CAR-positive viable T cells for patients 100 kg and above.

Tecartus is recommended to be infused 3 to 14 days after completion of the lymphodepleting chemotherapy for MCL patients. The availability of the treatment must be confirmed prior to starting the lymphodepleting regimen.

Pre-treatment (lymphodepleting chemotherapy) for MCL patients
- A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/m² and fludarabine 30 mg/m² must be administered prior to infusing Tecartus. The recommended days are on the 5^{th}, 4^{th}, and 3^{rd} day before infusion of Tecartus.

Acute lymphoblastic leukaemia
Treatment consists of a single dose for infusion containing a dispersion for infusion of CAR-positive viable T cells in one container. The target dose is 1×10^6 CAR-positive viable T cells per kg of body weight, with a maximum of 1×10^8 CAR-positive viable T cells for patients 100 kg and above.

Tecartus is recommended to be infused 2 to 14 days after completion of the lymphodepleting chemotherapy for ALL patients. The availability of the treatment must be confirmed prior to starting the lymphodepleting regimen.

Pre-treatment (lymphodepleting chemotherapy) for ALL patients
A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 900 mg/m^2 over 60 minutes must be administered prior to infusing Tecartus. This is recommended on the 2^{nd} day before

infusion of Tecartus. Fludarabine 25 mg/m^2 over 30 minutes must be administered prior to infusing Tecartus. The recommended days are on the 4th, 3rd, and 2nd day before infusion of Tecartus.

Mantle cell lymphoma and acute lymphoblastic leukaemia

Pre-medication
- To minimise potential acute infusion reactions, it is recommended that patients be pre-medicated with paracetamol 500 to 1,000 mg given orally and diphenhydramine 12.5 to 25 mg intravenous or oral (or equivalent) approximately 1 hour prior to infusion.
- Prophylactic use of systemic corticosteroids is not recommended (see section 4.5).

Monitoring prior to infusion
- In some patient groups at risk, a delay of the Tecartus infusion may be indicated (see section 4.4- Reasons to delay treatment).

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

Special populations

Elderly
No dose adjustment is required in patients ≥65 years of age.

Patients seropositive for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV)
There is no experience with manufacturing Tecartus for patients with a positive test for HIV, active HBV, or active HCV infection. Therefore, the benefit/risk has not yet been established in this population.

Paediatric population
Tecartus is not indicated for children and adolescents under 18 years old.
The safety and efficacy of Tecartus in children and adolescents aged less than 18 years have not yet been established. No data are available.

Method of administration

Tecartus is for intravenous use only.

Tecartus must not be irradiated. Do NOT use a leukodepleting filter.

Before administration, it must be confirmed that the patient's identity matches the unique patient information on the Tecartus infusion bag and cassette.

Administration
- A leukodepleting filter must not be used.
- Tocilizumab and emergency equipment must be available prior to infusion and during the monitoring period.
- For autologous use only, verify the patient ID to match the patient identifiers on the Tecartus bag.

- Once tubing has been primed, infuse the entire content of the Tecartus bag within 30 minutes by either gravity or a peristaltic pump.

For detailed instructions on preparation, administration, accidental exposure and disposal of Tecartus, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Contraindications of the lymphodepleting chemotherapy must be considered.

4.4 Special warnings and precautions for use

Traceability

The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability the name of the product, the batch number and the name of the treated patient must be kept for a period of 30 years.

Autologous use

Tecartus is intended solely for autologous use and must not, under any 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 cassette label does not match the intended patient's identity.

General

Warnings and precautions of lymphodepleting chemotherapy must be considered.

Monitoring after infusion

Patients must be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs/symptoms of CRS and/or neurologic events. After the first 10 days following infusion, the patient is to be monitored at the physician's discretion.

Counsel patients to remain within the proximity of a qualified treatment centre for at least 4 weeks following infusion and to seek immediate medical attention should signs or symptoms of CRS or neurological adverse reactions occur. Monitoring of vital signs and organ functions must be considered depending on the severity of the reaction.

Reasons to delay treatment

Due to the risks associated with Tecartus treatment, infusion must be delayed if a patient has any of the following conditions:
- Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions, or hypotension) including from preceding chemotherapies.
- Active uncontrolled infection or inflammatory disease.
- Active graft-versus-host disease (GvHD).

In some cases, the treatment may be delayed after administration of the lymphodepleting chemotherapy regimen. If the infusion is delayed for more than 2 weeks after the patient has received the lymphodepleting chemotherapy, lymphodepleting chemotherapy regimen must be administered again (see section 4.2)

Serological testing

Screening for HBV, HCV, and HIV must be performed before collection of cells for manufacturing of Tecartus (see section 4.2).

Blood, organ, tissue and cell donation

Patients treated with Tecartus must not donate blood, organs, tissues, or cells for transplantation.

Active central nervous system (CNS) lymphoma

There is no experience of use of this medicinal product in patients with active CNS lymphoma defined as brain metastases confirmed by imaging. In ALL, asymptomatic patients with a maximum of CNS-2 disease (defined as white blood cells <5/µL in cerebral spinal fluid with presence of lymphoblasts) without clinically evident neurological changes were treated with Tecartus, however, data is limited in this population. Therefore, the benefit/risk of Tecartus has not been established in these populations. Tecartus is not indicated for the treatment of patients with active central nervous system lymphoma.

Concomitant disease

Patients with a history of or active CNS disorder or inadequate renal, hepatic, pulmonary, or cardiac function were excluded from the studies. These patients are likely to be more vulnerable to the consequences of the adverse reactions described below and require special attention.

Cytokine release syndrome

Nearly all patients experienced some degree of CRS. Severe CRS, which can be fatal, was observed with Tecartus with a median time to onset of 3 days (range: 1 to 13 days). Patients must be closely monitored for signs or symptoms of these events, such as high fever, hypotension, hypoxia, chills, tachycardia and headache (see section 4.8). CRS is to be managed at the physician's discretion, based on the patient's clinical presentation and according to the CRS management algorithm provided in Table 1.

Diagnosis of CRS requires excluding alternate causes of systemic inflammatory response, including infection.

Management of cytokine release syndrome associated with Tecartus
At least 1 dose per patient of tocilizumab, an interleukin-6 (IL-6) receptor inhibitor, must be on site and available for administration prior to Tecartus infusion. The qualified treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose.

Treatment algorithms have been developed to ameliorate some of the CRS symptoms experienced by patients on Tecartus. These include the use of tocilizumab or tocilizumab and corticosteroids, as summarised in Table 1. Patients who experience Grade 2 or higher CRS (e.g. hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) must be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive-care supportive therapy.

CRS has been known to be associated with end organ dysfunction (e.g., hepatic, renal, cardiac, and pulmonary). In addition, worsening of underlying organ pathologies can occur in the setting of CRS. Patients with medically significant cardiac dysfunction must be managed by standards of critical care and measures such as echocardiography is to be considered. In some cases, macrophage activation syndrome (MAS) and haemophagocytic lymphohistiocytosis (HLH) may occur in the setting of CRS.

Evaluation for haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) is to be considered in patients with severe or unresponsive CRS.

Tecartus continues to expand and persist following administration of tocilizumab and corticosteroids. Tumour necrosis factor (TNF) antagonists are not recommended for management of Tecartus-associated CRS.

Table 1 CRS grading and management guidance

CRS Grade *(a)*	Tocilizumab	Corticosteroids
Grade 1 Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	If not improving after 24 hours, administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg).	N/A
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO_2 or hypotension responsive to fluids or low-dose of one vasopressor or Grade 2 organ toxicity *(b)*.	Administer tocilizumab *(c)* 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24 hour period; maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS, or if no response to second or subsequent doses of tocilizumab, consider alternative measures for treatment of CRS. If improving, discontinue tocilizumab.	If no improvement within 24 hours after starting tocilizumab, manage as per Grade 3. If improving, taper corticosteroids, and manage as Grade 1.
Grade 3 Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% FiO_2 or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis.	Per Grade 2	Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours) 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 or continuous veno-venous haemodialysis or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2	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.

N/A = not available/not applicable
(a) Lee et al 2014.
(b) Refer to Table 2 for management of neurologic adverse reactions.
(c) Refer to tocilizumab summary of product characteristics for details.

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 life-threatening or fatal. The median time to onset was 7 days (range: 1 to 262 days) following Tecartus infusion (see section 4.8).

Patients who experience Grade 2 or higher neurologic toxicity/ICANS must be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive-care supportive therapy for severe or life-threatening neurologic toxicity/ICANS. Non-sedating, anti-seizure medicines are to be

considered as clinically indicated for Grade 2 or higher adverse reactions. Treatment algorithms have been developed to ameliorate the neurologic adverse reactions experienced by patients on Tecartus. These include the use of tocilizumab (if concurrent CRS) and/or corticosteroids for moderate, severe, or life-threatening neurologic adverse reactions as summarised in Table 2.

Table 2 Neurologic adverse reaction/ICANS grading and management guidance

Grading assessment	**Concurrent CRS**	**No concurrent CRS**
Grade 2	Administer tocilizumab as per Table 1 for management Grade 2 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	Administer tocilizumab as per Table 1 for management of Grade 2 CRS. In addition, administer dexamethasone 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper corticosteroids. If improving, discontinue tocilizumab and manage as Grade 2. If still not improving, manage as Grade 4.	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.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 4	Administer tocilizumab as per Table 1 for management of Grade 2 CRS. Administer methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 more days. If 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.	

Infections and febrile neutropenia

Severe infections, which could be life-threatening, were very commonly observed with Tecartus (see section 4.8).

Patients must be monitored for signs and symptoms of infection before, during and after infusion and treated appropriately. Prophylactic antibiotics must be administered according to standard institutional guidelines.

Febrile neutropenia has been observed in patients after Tecartus infusion (see section 4.8) and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated.

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

Viral reactivation

Viral reactivation, e.g. Hepatitis B virus (HBV) reactivation, can occur in patients treated with medicinal products directed against B cells and could result in fulminant hepatitis, hepatic failure, and death.

Prolonged cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and Tecartus infusion and must be managed according to standard guidelines. Grade 3 or higher prolonged cytopenias following Tecartus infusion occurred very commonly and included thrombocytopenia, neutropenia, and anaemia (see section 4.8). Patient blood counts must be monitored after Tecartus infusion.

Hypogammaglobulinaemia

B-cell aplasia leading to hypogammaglobulinaemia can occur in patients receiving treatment with Tecartus. Hypogammaglobulinaemia was very commonly observed in patients treated with Tecartus (see section 4.8). Hypogammaglobulinaemia predisposes patients to have infections. Immunoglobulin levels should be monitored after treatment with Tecartus and managed using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement in case of recurrent infections and must be taken according to standard guidelines.

Hypersensitivity reactions

Serious hypersensitivity reactions including anaphylaxis, may occur due to DMSO or residual gentamicin in Tecartus.

Secondary malignancies including of T cell origin

Patients treated with Tecartus may develop secondary malignancies. T-cell malignancies have been reported following treatment of haematological malignancies with a BCMA- or CD19-directed CAR T-cell therapy. T-cell malignancies, including CAR-positive malignancies, have been reported within weeks and up to several years following administration of a CD19- or BCMA-directed CAR T-cell therapy. There have been fatal outcomes. Patients must 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.

Tumour lysis syndrome (TLS)

TLS, which may be severe, has occasionally been observed. To minimise risk of TLS, patients with elevated uric acid or high tumour burden should receive allopurinol, or an alternative prophylaxis, prior to Tecartus infusion. Signs and symptoms of TLS must be monitored, and events managed according to standard guidelines.

Prior stem cell transplantation (GvHD)

It is not recommended that patients who underwent an allogeneic stem cell transplant and suffer from active acute or chronic GvHD receive treatment because of the potential risk of Tecartus worsening GvHD.

Prior treatment with anti-CD19 therapy

Tecartus is not recommended if the patient has relapsed with CD19-negative disease after prior anti-CD19 therapy.

CD19-negative acute lymphoblastic leukaemia disease
Tecartus is not recommended for patients who have CD19-negative disease or an unconfirmed CD19 status.

Sodium content

This medicinal product contains 300 mg sodium per infusion, equivalent to 15% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No 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 therefore not recommended before infusion (see section 4.2).

Administration of corticosteroids as per the toxicity management guidelines does not impact the expansion and persistence of CAR T cells.

Live vaccines

The safety of immunisation with live viral vaccines during or following Tecartus treatment has not been studied. As a precautionary measure, 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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

The pregnancy status of women of childbearing potential must be verified before starting Tecartus treatment.

See the prescribing information for lymphodepleting chemotherapy 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.

Pregnancy

There are no available data with Tecartus use in pregnant women. No reproductive and developmental toxicity animal studies have been conducted with Tecartus to assess whether it can cause foetal harm when administered to a pregnant woman (see section 5.3).

It is not known if Tecartus has the potential to be transferred to the foetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause foetal toxicity, including B-cell lymphocytopenia. Therefore, Tecartus is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women must be advised on the potential risks to the foetus. Pregnancy after Tecartus therapy must be discussed with the treating physician.

Assessment of immunoglobulin levels and B-cells in newborn infants of mothers treated with Tecartus must be considered.

Breast-feeding

It is unknown whether Tecartus is excreted in human milk or transferred to the breast-feeding child. Breast-feeding women must be advised of the potential risk to the breast-fed child.

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.

4.7 Effects on ability to drive and use machines

Tecartus has major influence on the ability to drive and use machines.

Due to the potential for neurologic events, including altered mental status or seizures, patients must not drive or operate heavy or potentially dangerous machines until at least 8 weeks after infusion or until resolution of neurologic adverse reactions.

4.8 Undesirable effects

Summary of the safety profile

Mantle cell lymphoma
The safety data described in this section reflect exposure to Tecartus in ZUMA-2, a Phase 2 study 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) based on a recommended dose which was weight-based.

The most significant and frequently occurring adverse reactions were CRS (91%), infections (55%) and encephalopathy (51%).

Serious adverse reactions occurred in 56% of patients. The most common serious adverse reactions included encephalopathy (26%), infections (28%) and cytokine release syndrome (15%).

Grade 3 or higher adverse reactions were reported in 67% of patients. The most common Grade 3 or higher non-haematological adverse reactions included infections (34%) 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%).

Acute lymphoblastic leukaemia
The safety data described in this section reflect exposure to Tecartus in ZUMA-3, a Phase 1/2 study in which a total of 100 patients with relapsed/refractory B-cell precursor ALL received a single dose of CAR-positive viable T cells (0.5×10^6, 1×10^6, or 2×10^6 anti-CD19 CAR T cells/kg) based on a recommended dose which was weight based.

The most significant and frequently occurring adverse reactions were CRS (91%), encephalopathy (57%), and infections (41%).

Serious adverse reactions occurred in 70% of patients. The most common serious adverse reactions included CRS (25%), infections (22%) and encephalopathy (21%).

Grade 3 or higher adverse reactions were reported in 76% of patients. The most common Grade 3 or higher non-haematological adverse reactions included infections (27%), CRS (25%) and encephalopathy (22%).

Tabulated list of adverse reactions

Adverse reactions described in this section were identified in a total of 182 patients exposed to Tecartus in two multi-centre pivotal clinical studies, ZUMA-2 (n=82) and ZUMA-3 (n=100). These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3 Adverse drug reactions identified with Tecartus

System Organ Class (SOC)	**Frequency**	**Adverse reactions**
Infections and infestations		
	Very common	Unspecified pathogen infections Bacterial infections Fungal infections Viral Infections
Blood and lymphatic system disorders		
	Very common	Leukopenia[a] Neutropenia[a] Lymphopenia[a] Thrombocytopenia[a] Anaemia[a] Febrile neutropenia
	Common	Coagulopathy
Immune system disorders		
	Very common	Cytokine Release Syndrome[b] Hypogammaglobulinaemia
	Common	Hypersensitivity Haemophagocytic lymphohistiocytosis
Metabolism and nutrition disorders		
	Very common	Hypophosphataemia[a] Decreased appetite Hypomagnesaemia Hyperglycaemia[a]
	Common	Hypoalbuminemia[a] Dehydration
Psychiatric disorders		
	Very common	Delirium Anxiety Insomnia
Nervous system disorders		
	Very common	Encephalopathy Tremor Headache Immune effector cell-associated neurotoxicity syndrome (ICANS[b, c]) Aphasia Dizziness Neuropathy
	Common	Seizures, including status epilepticus Ataxia Increased intracranial pressure
Cardiac disorders		
	Very common	Tachycardias Bradycardias
	Common	Non-ventricular arrhythmias
Vascular disorders		
	Very common	Hypotension Hypertension

System Organ Class (SOC)	Frequency	Adverse reactions
		Haemorrhage
	Common	Thrombosis
Respiratory, thoracic and mediastinal disorders		
	Very common	Cough Dyspnoea Pleural effusion Hypoxia
	Common	Respiratory failure Pulmonary oedema
Gastrointestinal disorders		
	Very common	Nausea Diarrhoea Constipation Abdominal pain Vomiting Oral pain
	Common	Dry mouth Dysphagia
Skin and subcutaneous tissue disorders		
	Very common	Rash Skin disorder
Musculoskeletal and connective tissue disorders		
	Very common	Musculoskeletal pain Motor dysfunction
Renal and urinary disorders		
	Very common	Renal insufficiency
	Common	Urine output decreased
General disorders and administration site conditions		
	Very common	Oedema Fatigue Pyrexia Pain Chills
	Common	Infusion related reaction
Eye Disorders		
	Common	Visual impairment
Investigations		
	Very common	Alanine aminotransferase increased[a] Blood uric acid increased[a] Aspartate aminotransferase increased[a] Hypocalcaemia[a] Hyponatraemia[a] Direct bilirubin increased[a] Hypokalaemia[a]
	Common	Bilirubin increased[a]

Only cytopenias that resulted in (i) new or worsening clinical sequelae or (ii) that required therapy or (iii) adjustment in current therapy are included in Table 3.
[a] Frequency based on Grade 3 or higher laboratory parameter.
[b] See section Description of selected adverse reactions.
[c] The frequency of ICANS has been estimated from events reported in the post-marketing setting.
ZUMA-2 data cutoff: 24 July 2021; ZUMA-3 data cutoff: 23 July 2021

Description of selected adverse reactions from ZUMA-2 and ZUMA-3 (n=182), and from post marketing reporting

Cytokine release syndrome
CRS occurred in 91% of patients. Twenty percent (20%) of patients experienced Grade 3 or higher (severe or life-threatening) CRS. The median time to onset was 3 days (range: 1 to 13 days) and the

median duration was 9 days (range: 1 to 63 days). Ninety-seven percent (97%) of patients recovered from CRS.

The most common signs or symptoms associated with CRS among the patients who experienced CRS included pyrexia (94%), hypotension (64%), hypoxia (32%), chills (31%), tachycardia (27%), sinus tachycardia (23%), headache (22%), fatigue (16%), and nausea (13%). Serious adverse reactions that may be associated with CRS included hypotension (22%), pyrexia (15%), hypoxia (9%), tachycardia (3%), dyspnoea (2%) and sinus tachycardia (2%). See section 4.4 for monitoring and management guidance.

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

The most common neurologic adverse reactions including ICANS represented tremor (32%), confusional state (27%), encephalopathy (27%), aphasia (21%), and agitation (11%). Serious adverse reactions including encephalopathy (15%), aphasia (6%), confusional state (5%) and serious cases of cerebral oedema which may become fatal have occurred in patients treated with Tecartus. See section 4.4 for monitoring and management guidance.

Febrile neutropenia and infections
Febrile neutropenia was observed in 12% of patients after Tecartus infusion. Infections occurred in 87 of the 182 patients treated with Tecartus in ZUMA-2 and ZUMA-3. Grade 3 or higher (severe, life-threatening or fatal) infections occurred in 30% of patients including unspecified pathogen, bacterial, fungal and viral infections in 23%, 8%, 2% and 4% of patients respectively. See section 4.4 for monitoring and management guidance.

Prolonged cytopenias
Cytopenias are very common following prior lymphodepleting chemotherapy and Tecartus therapy.

Prolonged (present on or beyond Day 30 or with an onset at Day 30 or beyond) Grade 3 or higher cytopenias occurred in 48% of patients and included neutropenia (34%), thrombocytopenia (27%) and anaemia (15%). See section 4.4 for management guidance.

Hypogammaglobulinaemia
Hypogammaglobulinaemia occurred in 12% of patients. Grade 3 or higher hypogammaglobulinemia occurred in 1% of patients. See section 4.4 for management guidance.

Immunogenicity

The immunogenicity of Tecartus 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 anti-CD19 CAR T-cell antibody immunogenicity has been observed in MCL patients. Based on an initial screening assay, 17 patients in ZUMA-2 at any time point tested positive for antibodies; however, a confirmatory orthogonal cell-based assay demonstrated that all 17 patients in ZUMA-2 were antibody negative at all time points tested. Based on an initial screening assay, 16 patients in ZUMA-3 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 positive antibody result at retreatment Day 28 and Month 3. There is no

evidence that the kinetics of initial expansion, CAR T-cell function and persistence of Tecartus, or the safety or effectiveness of Tecartus, were altered in these patients.

Secondary malignancies

There have been cases of the following adverse effect(s) reported after treatment with other CAR T-cell products, which might also occur after treatment with Tecartus: secondary malignancy of T-cell origin.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il.

4.9 Overdose

There are no data regarding the signs of overdose with Tecartus.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, antineoplastic cell and gene therapy, ATC code: L01XL06.

Mechanism of action

Tecartus, a CD19-directed genetically modified autologous T-cell immunotherapy, binds to CD19 expressing cancer cells and normal B cells. Following anti-CD19 CAR T-cell engagement with CD19 expressing target cells, the CD28 co-stimulatory domain and CD3-zeta signalling domain activate downstream signalling 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.

Pharmacodynamic effects

In both ZUMA-2 and ZUMA-3, 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, interferon-gamma (IFN-γ) and IL-2 receptor alpha were analysed. Peak elevation was generally observed within the first 8 days after infusion and levels generally returned to baseline within 28 days.

Due to the on target, off-tumour effect of Tecartus a period of B-cell aplasia may occur following treatment.

Translational analyses performed to identify associations between cytokine levels and incidence of CRS or neurologic events showed that higher levels (peak and AUC at 1 month) of multiple serum analytes, including IL-6, IL-10 and TNF-α, were associated with Grade 3 or higher neurologic adverse reactions and Grade 3 or higher CRS.

Clinical efficacy and safety

Relapsed or refractory MCL: ZUMA-2
The efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL who had previously received anthracycline or bendamustine-containing chemotherapy, an anti CD20 antibody,

and a Bruton's tyrosine kinase inhibitor (BTKi) (ibrutinib or acalabrutinib), was evaluated in a phase 2 single-arm, open-label, multi-centre trial. Eligible patients also had disease progression after last regimen or refractory disease to the most recent therapy. Patients with active or serious infections, prior allogeneic haematopoietic stem cell transplantation (HSCT), detectable cerebrospinal fluid malignant cells or brain metastases, and any history of CNS lymphoma or CNS disorders were ineligible. In ZUMA-2, a total of 74 patients were enrolled (*i.e.* leukapheresed) and 68 of these patients were treated with Tecartus. Three patients did not receive Tecartus due to manufacturing failure. Two other patients were not treated due to progressive disease (death) following leukapheresis. One patient was not treated with Tecartus after receiving lymphodepleting chemotherapy due to ongoing active atrial fibrillation. The full analysis set (FAS) was defined as all patients who underwent leukapheresis. A summary of the patient baseline characteristics is provided in Table 4.

Table 4 Summary of baseline characteristics for ZUMA-2

Category	**All leukapheresed (FAS) (N=74)**
Age (years)	
Median (min, max)	65 (38, 79)
≥ 65	58%
Male gender	84%
Median number of prior therapies (min, max)	3 (1; 5)
Relapsed/refractory subgroup	
Relapsed after auto-SCT	42%
Refractory to last MCL therapy	39%
Relapsed after last MCL therapy	19%
Patients with disease stage IV	86%
Patients with bone marrow involvement	51%
Morphological characteristic	
Classical MCL	54%
Blastoid MCL	26%
Other	1%
Unknown	19%
Received bridging therapy	
Yes	38%
No	62%
Ki-67 IHC by central laboratory	
N	49
Median	65%
Auto-SCT, autologous stem cell transplant; IHC, immunohistochemistry; Max, maximum; MCL, mantle cell lymphoma; Min, minimum.	

Tecartus was administered to patients as a single intravenous infusion at a target dose of 2×10^6 anti-CD19 CAR T cells/kg (maximum permitted dose: 2×10^8 cells) after lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m² intravenously and fludarabine 30 mg/m² intravenously, both given on the 5th, 4th, and 3rd day before treatment. Bridging therapy between leukapheresis and lymphodepleting chemotherapy was permitted to control disease burden.

For patients treated with Tecartus, the median time from leukapheresis to product release was 13 days (range: 9 to 20 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). The median dose was 2.0×10^6 anti-CD19 CAR T cells/kg. All patients received Tecartus infusion on day 0 and were hospitalized until day 7 at the minimum.

The primary endpoint was objective response rate (ORR) as determined by Lugano 2014 criteria by an independent review committee. Secondary endpoints included duration of response (DOR), overall survival (OS), progression free survival (PFS) and severity of adverse events.

For the primary analysis, the analysis set 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%. The ORR was significantly higher than the prespecified historical control rate of 25% at a 1-sided significance level of 0.025 ($p < 0.0001$).

The updated 24-month follow-up analyses of efficacy were conducted using the modified intent to treat (mITT) analysis set, which consisted of 68 patients treated with Tecartus. In the 24-month follow up analysis, the ORR and CR rates in the 68 patients in the mITT analysis set were 91% and 68% respectively.

Results in the FAS from both the primary analysis and 24-month follow-up analysis are shown in Table 5.

Table 5 Summary of efficacy results for ZUMA-2

Category	**All leukapheresed [a](FAS) (N = 74)**	
	Primary Analysis	**24-month Follow-Up**
Objective response rate (ORR), n (%) [95% CI]	**62 (84%)** [73.4, 91.3]	**62 (84%)** [73.4, 91.3]
CR n (%) [95% CI]	44 (59%) [47.4, 70.7]	46 (62%) [50.1, 73.2]
PR n (%) [95% CI]	18 (24%) [15.1, 35.7]	16 (22%)[12.9, 32.7]
Duration of response (DOR)[b]		
Median in months [95% CI]	NR [10.4, NE]	28.2 (13.5, 47.1)
Range [c] in months	0.0+, 35.0+	0.0+, 53.0+
Ongoing responses, CR+PR, CR, n (%) [d]	32 (43%), 30 (41%)	25 (34%), 25 (34%)
Progression free survival		
Median, months [95% CI]	16.2 [9.9, NE]	24.0 (10.1, 48.2)

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

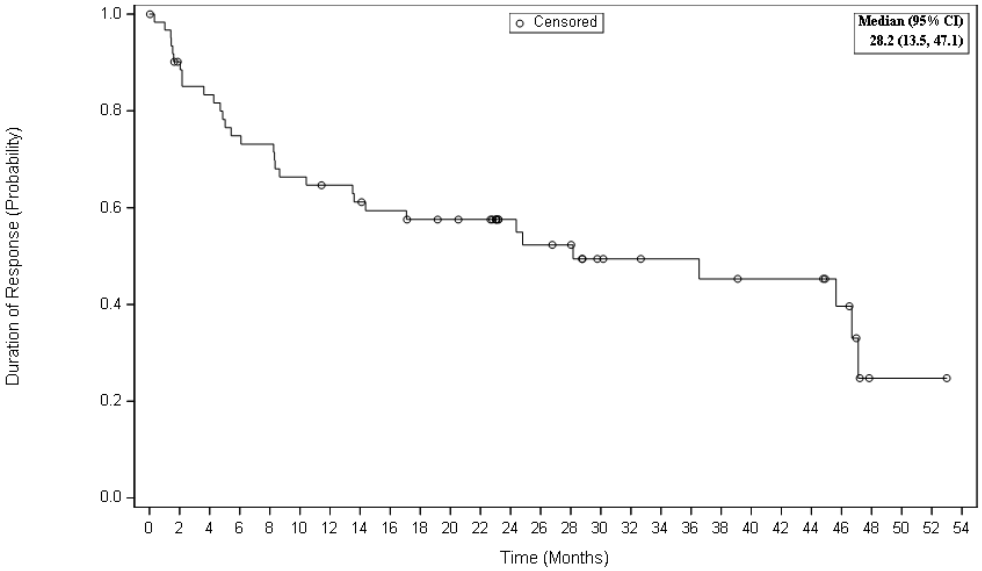
a Of the 74 patients that were enrolled (*i.e.* leukapheresed), 69 patients received lymphodepleting chemotherapy, and 68 patients received Tecartus.

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.

d At the data cutoff date. Percentages are calculated using the total number of patients in the analysis set as the denominator.

Figure 1 Kaplan Meier DOR in the FAS



Relapsed or refractory B-cell precursor ALL: ZUMA-3
A Phase 2, open-label, multicenter trial evaluated the efficacy and safety of Tecartus in adult patients with relapsed or refractory 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, and any history of CNS disorders. Patients with CNS-2 disease without clinically evident neurologic changes were eligible. In ZUMA-3 Phase 2, a total of 71 patients were enrolled (i.e. leukapheresed) and 55 patients were treated with Tecartus. Six patients did not receive Tecartus due to manufacturing failure. Eight other patients were not treated, primarily due to AEs 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 FAS included all patients who underwent leukapheresis and the modified intent to treat (mITT) analysis set includes all patients leukapheresed and treated with Tecartus in Phase 2. A summary of patient baseline characteristics is provided in Table 6.

Table 6 Summary of baseline characteristics for ZUMA-3 Phase 2

Category	**All leukapheresed (FAS) (N=71)**	**All treated (mITT) (N=55)**
Age (years)		
Median (min, max)	44 (19 to 84)	40 (19 to 84)
Male gender	58%	60%
White ethnicity	72%	67%
Primary refractory disease	30%	33%
Relapsed/refractory disease after ≥ 2 lines of therapy	76%	78%
First relapse if first remission ≤ 12 months	28%	29%

Category	All leukapheresed (FAS) (N=71)	All treated (mITT) (N=55)
Number of Lines of Prior Therapy		
Median (min, max)	2 (1 to 8)	2 (1 to 8)
≥ 3	48%	47%
Prior Therapies		
Allo-SCT	39%	42%
Blinatumomab	46%	45%
Inotuzumab	23%	22%
Philadelphia chromosome (Ph^+)	27%	27%
Allo-SCT, allogenic stem cell transplant; Max, maximum; Min, minimum		

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 cyclophosphamide 900 mg/m^2 intravenously over 60 mins on the 2nd day before Tecartus infusion and fludarabine 25 mg/m^2 intravenously over 30 mins on the 4th, 3rd, and 2nd day before Tecartus infusion. Of the 55 patients who received Tecartus, 51 patients received bridging therapy between leukapheresis and lymphodepleting chemotherapy to control disease burden.

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). The median dose was 1.0×10^6 anti-CD19 CAR T cells/kg. All patients received Tecartus infusion on day 0 and were hospitalized until day 7 at the minimum.

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. In the 55 patients treated with Tecartus (mITT), the OCR rate was 70.9% with a CR rate of 56.4% (Table 7), which was significantly greater than the prespecified control rate of 40%. Among the 39 patients who achieved a CR or CRi, the median time to response was 1.1 months (range: 0.85 to 2.99 months).

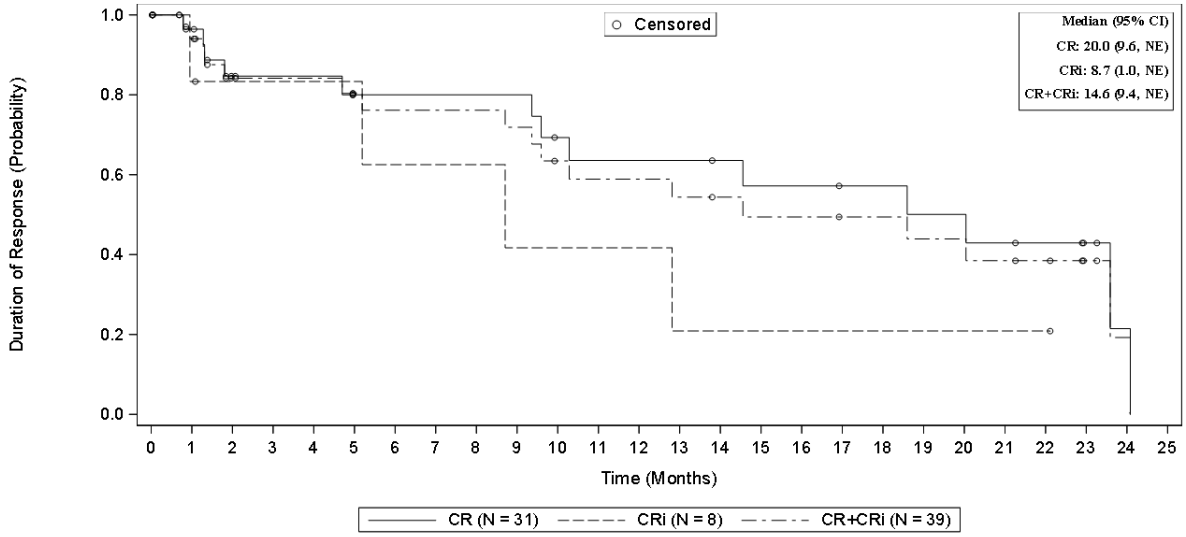
All treated patients had potential follow-up for ≥ 18 months with a median follow-up time of 20.5 months (95% CI: 0.3, 32.6 months) and a median follow-up time for OS of 24.0 months (95% CI: 23.3, 24.6).

Table 7 Summary of efficacy results for ZUMA3 Phase 2

	FAS N = 71	mITT[a] N = 55
OCR rate (CR + CRi) n (%) [95% CI]	39 (54.9) [43, 67]	39 (70.9) [57.0, 82.0]
CR rate, n (%) [95% CI]	31 (43.7) [32, 56]	31 (56.4) [42.0, 70.0]
Minimal Residual Disease (MRD) negative rate among OCR (CR or CRi) patients, n (%)	n = 39 38 (97%)	n = 39 38 (97%)
Duration of Remission, median in months [95% CI] [b] Median range in months	14.6 [9.4, NE][c] (0.03+, 24.08+)	14.6 [9.4, NE][c] (0.03+, 24.08+)
CI, confidence interval; CR, complete remission; NE, not estimable		

a. Of the 71 patients that were enrolled (and leukapheresed), 57 patients received conditioning chemotherapy, and 55 patients received Tecartus.
b. Subjects were censored at their last evaluable disease assessment before initiation of a new anticancer therapy (excluding resumption of a tyrosine kinase inhibitor) or allo-SCT to exclude any contribution that the new therapy might have on DOR that could confound the contribution of KTE-X19. The results of the analyses that did not censor for subsequent allo-SCT or the initiation of new anti-cancer therapy were consistent with the analyses that did censor the events.
c. The duration of remission was defined only for subjects achieving an OCR, therefore the results of the analysis in the FAS and mITT were identical.

Figure 2 Kaplan Meier DOR in the mITT Analysis Set[a]



a. The DOR was defined only for subjects achieving an OCR, therefore the results of the analysis in the FAS and mITT were identical.

5.2 Pharmacokinetic properties

Cellular kinetics

Mantle cell lymphoma
Following infusion 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 the infusion.

Among patients with MCL, the number of anti-CD19 CAR T cells in blood was associated with objective response (CR or PR) (Table 8).

Table 8 Summary of brexucabtagene autoleucel pharmacokinetics in ZUMA-2

Number of anti-CD19 CAR T cell	**Responding patients (CR or PR) (N=63)**	**Non-responding patients (N=5)**	**P-Value**
Peak (cells/µL) Median [min; max], n	97.52 [0.24, 2 589.47], 62	0.39 [0.16, 22.02], 5	0.0020
$AUC_{0–28}$ (cells/µL·day) Median [min; max], n	1 386.28 [3.83 to 2.77×10^4], 62	5.51 [1.81, 293.86], 5	0.0013

P-value is calculated by Wilcoxon test

Median peak anti-CD19 CAR T-cell values were 74.08 cells/µL in MCL patients ≥65 years of age (n=39) and 112.45 cells/µL in MCL patients <65 years of age (n=28). Median anti-CD19 CAR T-cell AUC values were 876.48 cells/µL·day in MCL patients ≥65 years of age and 1 640.21 cells/µL·day in MCL patients <65 years of age.

Acute lymphoblastic leukaemia
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 3 months. Median time to peak levels of anti-CD19 CAR T cells was within the first 15 days after Tecartus infusion.

A summary of the Tecartus pharmacokinetics over time, based on central assessment by overall response, is provided in Table 9.

Table 9 Summary of brexucabtagene autoleucel pharmacokinetics in ZUMA-3 Phase 2

Number of anti-CD19 CAR T cell	Patients with overall complete remission (CR/CRi) (N=39)	Patients with non-complete remission[a] (N=16)	P-Value
Peak (cells/µL) Median [min; max], n	38.35 [1.31, 1 533.4], 36[b]	0.49 [0.00, 183.50], 14[b]	0.0001[c]
$AUC_{0–28}$ (cells/µL·day) Median [min; max], n	424.03 [14.12 to 19 390.42], 36[b]	4.12 [0.00, 642.25], 14[b]	0.0001[c]

a. Three of 39 subjects who achieved CR or CRi and 2 of 16 subjects who were non-CR/CRi had no anti-CD19 CAR T-cell data at any post infusion visit.
b. Noncomplete remission includes all non-CR/CRi subjects whose response is classified incomplete remission response with partial hematologic recovery, blast-free hypoplastic or aplastic bone marrow (N = 4), partial response (N = 0), no response (N = 9), or not evaluable (N = 3).
c. P-value is calculated by Wilcoxon test

Median peak anti-CD19 CAR T-cell values were 34.8 cells/µL in ALL patients ≥65 years of age (n=8) and 17.4 cells/µL in ALL patients <65 years of age (n=47). Median anti-CD19 CAR T-cell AUC values were 425.0 cells/µL·day in ALL patients ≥65 years of age and 137.7 cells/µL·day in ALL patients <65 years of age.

In MCL and ALL patients, gender had no significant impact on $AUC_{Day\ 0–28}$ and C_{max} of Tecartus.

Studies of Tecartus in patients with hepatic and renal impairment were not conducted.

5.3 Preclinical safety data

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 medicinal product development were not performed.

No carcinogenicity or genotoxicity studies have been conducted.

No studies have been conducted to evaluate the effects of this treatment on fertility, reproduction, and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cryostor CS10 (contains DMSO)
Sodium chloride
Human albumin

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Tecartus is stable for 1 year when stored frozen in the vapour phase of liquid nitrogen (≤ − 150°C).

Tecartus is stable at room temperature (20 °C to 25 °C) for up to 3 hours after thawing. However, Tecartus infusion must begin within 30 minutes of thaw completion and the total infusion time should not exceed 30 minutes.

6.4 Special precautions for storage

Tecartus must be stored in the vapour phase of liquid nitrogen (≤ − 150 °C) and must remain frozen until the patient is ready for treatment to ensure viable live autologous cells are available for patient administration.

Tecartus may be stored a single time at -80 °C (± 10 °C), for up to 90 days. After storage at -80 °C (± 10 °C), the product must be used within the 90-day period or the labelled expiration date, whichever comes first. After these dates, the product must not be used and must be discarded.

Thawed product must not be refrozen.

For storage conditions after thawing of the medicinal product, see section 6.3.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Ethylene-vinyl acetate cryostorage bag with sealed addition tube and two available spike ports, containing approximately 68 mL of cell dispersion.

One cryostorage bag is individually packed in a shipping metal cassette.

6.6 Special precautions for disposal and other handling

Irradiation could lead to inactivation of the product.

Precautions to be taken before handling or administrating the medicinal product

Tecartus must be transported within the facility in closed, break-proof, leak-proof containers.

This medicinal product contains human blood cells. Healthcare professionals handling Tecartus must take appropriate precautions (wearing gloves and eye protection) to avoid potential transmission of infectious diseases.

Preparation prior to administration

- Verify that the patient's identity (ID) matches the patient identifiers on the Tecartus metal cassette.
- The Tecartus infusion bag must not be removed from the metal cassette if the information on the patient specific label does not match the intended patient.
- Once the patient ID is confirmed, remove the infusion bag from the metal cassette.

- Check that the patient information on the metal cassette label matches that on the infusion bag label.
- Inspect the infusion bag for any breaches of container integrity before thawing. If the infusion bag is compromised, follow the local guidelines for handling of waste of human derived material (and immediately contact Kite).

Thawing

- Place the infusion bag inside a second bag.
- Thaw Tecartus 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 infusion bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the infusion bag. Small clumps of cellular material should disperse with gentle manual mixing. Tecartus must not be washed, spun down, and/or re-suspended in new media prior to infusion. Thawing should take approximately 3 to 5 minutes.
- Once thawed, Tecartus is stable at room temperature (20 °C – 25 °C) for up to 3 hours. However, Tecartus infusion must begin within 30 minutes of thaw completion.

Administration

- For autologous single use only.
- Tocilizumab and emergency equipment must be available prior to infusion and during the monitoring period.
- A leukodepleting filter must not be used.
- Central venous access is recommended for the administration of Tecartus.
- Verify the patient ID again to match the patient identifiers on the Tecartus infusion bag.
- Prime the tubing with sodium chloride 9 mg/mL (0.9%) solution for injection (0.154 mmol sodium per mL) prior to infusion.
- Infuse the entire content of the Tecartus infusion bag within 30 minutes by either gravity or a peristaltic pump.
- Gently agitate the infusion bag during infusion to prevent cell clumping.
- After the entire content of the infusion bag is infused, rinse the tubing at the same infusion rate with sodium chloride 9 mg/mL (0.9%) solution for injection (0.154 mmol sodium per mL) to ensure all the treatment is delivered.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and all material that has been in contact with Tecartus (solid and liquid waste) must be handled and disposed of as potentially infectious waste in accordance with local guidelines on the handling of waste of human derived material.

Accidental exposure
In case of accidental exposure to Tecartus local guidelines on handling of human-derived material must be followed. Work surfaces and materials which have potentially been in contact with Tecartus must be decontaminated with appropriate disinfectant.

7. MANUFACTURER

Kite Pharma, Inc.
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El Segundo, CA 90245
USA

8. REGISTRATION HOLDER

Gilead Sciences Israel Ltd.
4 HaHarash Street
Hod Hasharon
4524075
Israel

Revised in December 2025.

Reference: EU SmPC November 2025

IL-DEC25-EU-NOV25