ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

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

A clear to opaque, white to red dispersion.

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.

Acute lymphoblastic leukaemia

Tecartus is indicated for the treatment of adult patients 26 years of age and above 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. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, suitable alternative measures to treat CRS instead of tocilizumab must be available prior to infusion.

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 infusion bag. The target dose is 2×10^6 CAR-positive viable T cells per kg of body weight (range: 1×10^6–2×10^6 cells/kg), with a 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 (i.e. date of product availability for shipment).

Pre-treatment (lymphodepleting chemotherapy) for MCL patients
- A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/m² intravenously and fludarabine 30 mg/m² intravenously 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 infusion bag. 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 (i.e. date of product availability for shipment).

Pre-treatment (lymphodepleting chemotherapy) for ALL patients
A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 900 mg/m^2 intravenously over 60 minutes must be administered prior to infusing Tecartus. This is recommended on the 2nd day before infusion of Tecartus. Fludarabine 25 mg/m^2 intravenously 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 intravenously or orally (or equivalent medicinal products) approximately 1 hour before the infusion of Tecartus.
- 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 7 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians can consider hospitalisation for the first 7 days or at the first signs or symptoms of CRS and/or neurologic events.
- After the first 7 days following the infusion, the patient is to be monitored at the physician's discretion.
- Patients must remain within proximity 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
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. In the exceptional case where tocilizumab is not available due to a shortage

that is listed in the European Medicines Agency shortage catalogue, suitable alternative measures to treat CRS instead of tocilizumab must be available prior to infusion.
- For autologous use only, verify the patient ID to match the patient identifiers on the Tecartus infusion bag.
- Once tubing has been primed, infuse the entire content of the Tecartus infusion 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.

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)

Monitoring after infusion

Patients must be monitored daily for the first 7 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians can consider hospitalisation for the first 7 days or at the first signs or symptoms of CRS and/or neurologic events. After the first 7 days following infusion, the patient is to be monitored at the physician's discretion.

Patients must remain within proximity of a qualified treatment centre for at least 4 weeks following infusion and 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.

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.

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). 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. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, the treatment centre must have access to suitable alternative measures instead of tocilizumab to treat CRS.

The management of patients should be conducted based on the patient's clinical presentation and in accordance with applicable local institutional and/or national or European/international clinical guidelines. Physicians are advised to exercise clinical judgment consistent with these standards.

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. HLH/MAS should be managed per local institutional and/or national or European/international clinical guidelines.

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.

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).

The management of patients should be conducted based on the patient's clinical presentation and in accordance with applicable local institutional and/or national or European/international clinical guidelines. Physicians are advised to exercise clinical judgment consistent with these standards.

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.

Long-term follow up
Patients are expected to enrol in a registry in order to better understand the long-term safety and efficacy of Tecartus.

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 1 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]

System Organ Class (SOC)	Frequency	Adverse reactions
		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 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

System Organ Class (SOC)	Frequency	Adverse reactions
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 1**.**

[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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 2.

Table 2 Summary of baseline characteristics for ZUMA-2

Category	**All leukapheresed (FAS) (N=74)**
Age (years)	
Median (min, max)	65 (38, 79)
≥ 65	58%

Category	All leukapheresed (FAS) (N=74)
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 3.

Table 3 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.

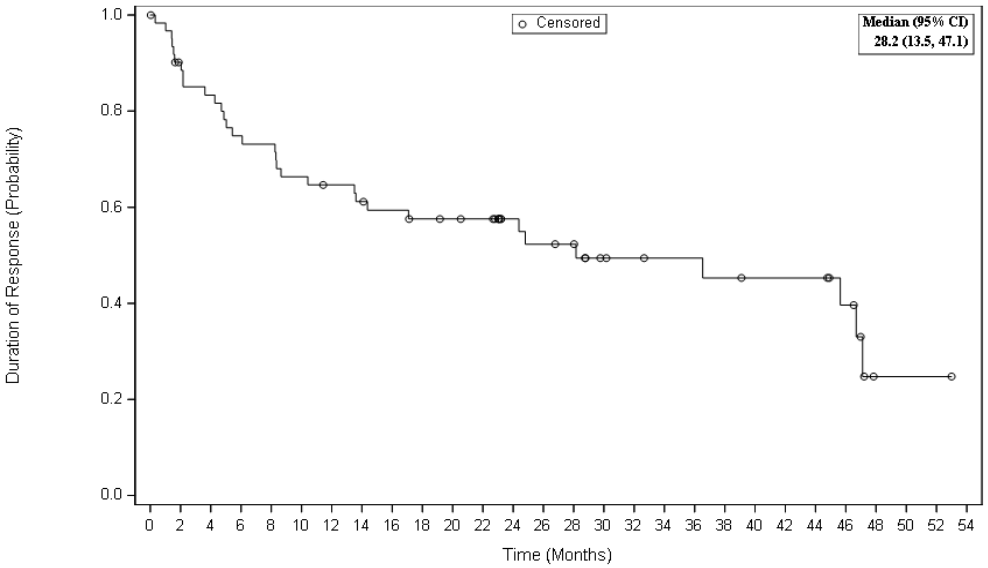
a Of the 74 patients that were enrolled (*i.e.* leukapheresed), 69 patients received lymphodepleting chemotherapy, and 68 patients received Tecartus.

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



Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Tecartus in all subsets of the paediatric population in treatment of MCL (see section 4.2 for information on paediatric use).

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 4.

Table 4 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%
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 5), 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 5 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+)

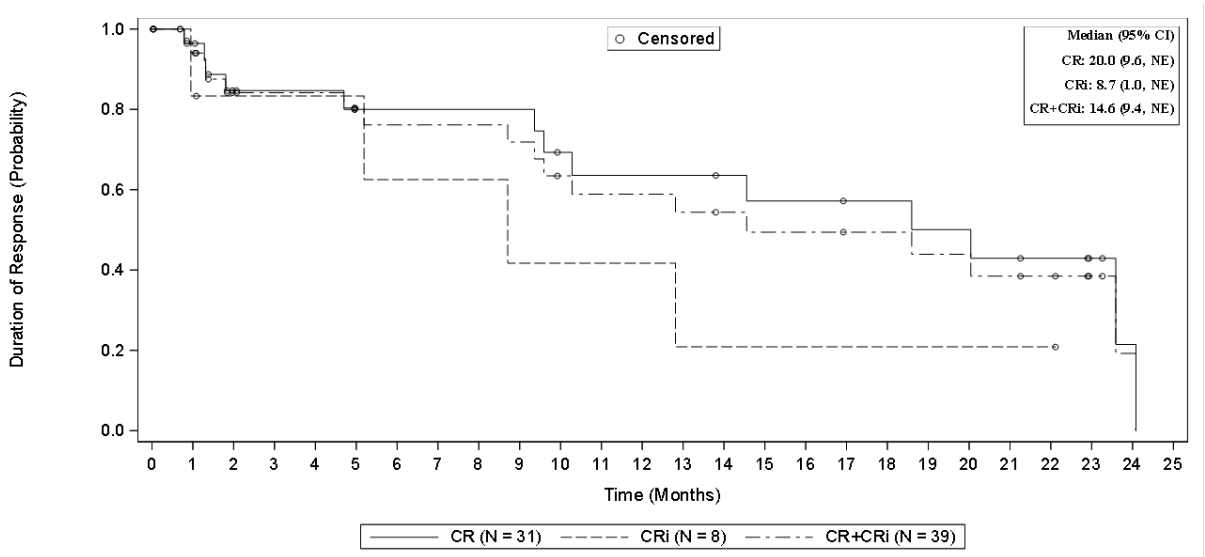
CI, confidence interval; CR, complete remission; NE, not estimable

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.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Tecartus in one or more subsets of the B-cell ALL paediatric population and waived the obligation to submit the results of studies with Tecartus for the treatment of ALL in the paediatric population weighing less than 6kg. See section 4.2 for information on paediatric use.

Conditional Approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme.
This means that further evidence on this medicinal product is awaited in both the MCL and ALL patient population.
The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

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 6).

Table 6 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 7.

Table 7 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 postinfusion 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. .Pvalue 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

1 year.

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 administering 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. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, suitable alternative measures to treat CRS instead of tocilizumab must be available prior to infusion.
- 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. MARKETING AUTHORISATION HOLDER

Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

8. MARKETING AUTHORISATION NUMBER

EU/1/20/1492/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 December 2020
Date of latest renewal: 26 February 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Kite Pharma, Inc.
2355 Utah Avenue
El Segundo
California
CA 90245
United States

Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

Name and address of the manufacturer responsible for batch release

Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Key elements:

Availability of tocilizumab and site qualification

The MAH will ensure that hospitals and their associated centres that dispense Tecartus are qualified in accordance with the agreed controlled distribution programme by:

- ensuring immediate, on-site access to one dose of tocilizumab per patient prior to Tecartus infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensuring that suitable alternative measures to treat CRS instead of tocilizumab are available on-site.
- ensuring healthcare professionals (HCP) involved in the treatment of a patient have completed the educational programme.
- as part of site qualification training, ensuring HCPs are made aware of the need to contact the MAH to obtain recommendations for tumour sample collection and testing following the development of a secondary malignancy.

Educational program – Prior to the launch of Tecartus in each Member State the MAH must agree the content and format of the educational materials with the National Competent Authority.

HCP Educational program

The MAH shall ensure that in each Member State where Tecartus is marketed, all HCPs who are expected to prescribe, dispense, and administer Tecartus shall be provided with a guidance document to:

- provide information about the safety and efficacy long-term follow up study and the importance of contributing to such a study
- facilitate identification of CRS and serious neurologic adverse reactions, including ICANS.
- facilitate management of the CRS and serious neurologic adverse reactions, including ICANS, consistent with applicable local institutional and/or national or European/international clinical guidelines.
- ensure adequate monitoring of CRS and serious neurologic adverse reactions, including ICANS.
- facilitate provision of all relevant information to patients
- ensure that adverse reactions are adequately and appropriately reported
- before treating a patient, ensure that at least 1 dose of tocilizumab for each patient is available on site. The qualified treatment centre must have access to additional doses of tocilizumab within 8 hours; in the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensure that suitable alternative measures to treat CRS are available on site
- inform on the risk of secondary malignancy of T-cell origin

Patient Educational program

To inform and explain to patients:

- the risks of CRS and serious neurologic adverse reactions, associated with Tecartus
- the need to report the symptoms to their treating doctor immediately
- the need to remain in the proximity of the location where Tecartus was received for at least 4 weeks following Tecartus infusion
- the need to carry the patient alert card at all times

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to further characterise the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory (r/r) mantle cell Lymphoma (MCL) and adult patients with r/r acute lymphoblastic leukaemia (ALL) the MAH shall conduct and submit the results of a prospective study based on data from a registry, according to an agreed protocol.	MCL: 31 March 2043 ALL: 31 December 2042

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL and the Benefit/Risk balance in the female, elderly and severely diseased patients, the MAH shall submit the results of a prospective study investigating efficacy and safety based on data from the same registry used to characterise the long-term efficacy and safety of Tecartus, according to an agreed protocol.	30 April 2027
In order to confirm the long-term efficacy and safety of Tecartus in adult patients with r/r ALL, the MAH should conduct and submit the results of a prospective, observational study based on data from a registry, according to an agreed protocol.	31 December 2027

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

METAL CASSETTE

1. NAME OF THE MEDICINAL PRODUCT

Tecartus 0.4 – 2 × 10^8 cells dispersion for infusion
brexucabtagene autoleucel (CAR+ viable T cells)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Autologous human T cells transduced with retroviral vector encoding an anti-CD19 chimeric antigen receptor (CAR).
This medicine contains cells of human origin.

Contains: 0.4 to 2 × 10^8 CAR+ viable T cells.

3. LIST OF EXCIPIENTS

Excipients: Cryostor CS10 (contains DMSO), human albumin, sodium chloride.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion
One sterile infusion bag.
Contents: approximately 68 mL of cell dispersion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not irradiate.
Gently mix the contents of the bag while thawing.
Do NOT use a leukodepleting filter.
STOP confirm patient ID prior to infusion.
Read the package leaflet before use.
For intravenous use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For autologous use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store frozen in vapour phase of liquid nitrogen ≤ − 150 °C or as indicated in the package leaflet.
Do not refreeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human blood cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1492/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot:
Kite Patient ID:
Additional Patient ID:
Patient Name:
Patient DOB:
SEC:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

INFUSION BAG

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Tecartus 0.4 – 2 × 10^8 cells dispersion for infusion
brexucabtagene autoleucel (CAR+ viable T cells)
For intravenous use only.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot:
Kite Patient ID:
Additional Patient ID:
Patient Name:
Patient DOB:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Contents: approximately 68 mL of cell dispersion.

6. OTHER

For autologous use only.
Verify patient ID.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Tecartus 0.4 – 2 × 10^8 cells dispersion for infusion
brexucabtagene autoleucel (CAR+ viable T cells)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- 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.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tecartus is and what it is used for

Tecartus is a gene therapy medicine used for treating mantle cell lymphoma and B-cell acute lymphoblastic leukaemia in adults. It is used when other medicines have stopped working for you (relapsed or refractory disease). The medicine is made specially for you from your own white blood cells that have been modified and is known as brexucabtagene autoleucel.

Mantle cell lymphoma and B-cell acute lymphoblastic leukaemia are cancers of a part of the immune system (the body's defences). They affect a type of white blood cell called B-lymphocytes. In both mantle cell lymphoma and B-cell acute lymphoblastic leukaemia, B-lymphocytes grow in an uncontrolled way and build up in the lymph tissue, bone marrow or blood.

How Tecartus works

The white blood cells are taken from your blood and are genetically modified so that they can target the cancer cells in your body. When Tecartus is infused into your blood, the modified white blood cells will kill the cancer cells.

2. What you need to know before you are given Tecartus

You must not be given Tecartus
- if you are allergic to any of the ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.
- if you can't receive the medicine to reduce the number of white blood cells in your blood (*lymphodepleting chemotherapy*) (see also section 3, How Tecartus is given).

Warnings and precautions

Tecartus is made from your own white blood cells and must only be given to you (*autologous use*).

Patients treated with Tecartus may develop new types of cancers. There have been reports of patients developing cancer, beginning in a type of white blood cells called T-cells, after treatment with other similar medicines. Talk to your doctor if you experience any new swelling of your glands (lymph nodes) or changes in your skin such as new rashes or lumps.

Tests and checks

Before you are given Tecartus your doctor will:
- Check your lungs, heart, kidney and blood pressure.
- Look for signs of infection or inflammation; and decide whether you need to be treated before you are given Tecartus.
- Check if your cancer is getting worse.
- Look for signs of graft-versus-host disease that can happen after a transplant. This happens when transplanted cells attack your body, causing symptoms such as rash, nausea, vomiting, diarrhoea and bloody stools.
- Check your blood for uric acid and for how many cancer cells there are in your blood. This will show if you are likely to develop a condition called *tumour lysis syndrome*. You may be given medicines to help prevent the condition.
- Check for hepatitis B, hepatitis C or HIV infection.
- Check if you had a vaccination in the previous 6 weeks or are planning to have one in the next few months.
- Check if you have previously received a treatment that attaches to the protein called CD19.

In some cases, it might not be possible to go ahead with the planned treatment with Tecartus. If Tecartus infusion is delayed for more than 2 weeks after you have received lymphodepleting chemotherapy you may have to receive more chemotherapy (see also section 3, How Tecartus is given).

After you have been given Tecartus

Tell your doctor or nurse immediately or get emergency help right away if you have any of the following:
- Chills, extreme tiredness, weakness, dizziness, headache, cough, shortness of breath, rapid or irregular heartbeat, severe nausea, vomiting, or diarrhoea which may be symptoms of a condition known as *cytokine release syndrome.* Take your temperature twice a day for 3 to 4 weeks after treatment with Tecartus. If your temperature is high, see your doctor immediately.
- Fits, shaking, or difficulty speaking or slurred speech, loss of consciousness or decreased level of consciousness, confusion and disorientation, loss of balance or coordination.
- Fever (e.g. temperature above 38°C), which may be a symptom of an infection.
- Extreme tiredness, weakness and shortness of breath, which may be symptoms of a lack of red blood cells.
- Bleeding or bruising more easily, which may be symptoms of low levels of cells in the blood known as platelets.

If any of the above apply to you (or you are not sure), talk to your doctor or nurse.

Your doctor will regularly check your blood counts as the number of blood cells and other blood components may decrease.

You may be asked to enrol in a registry for at least 15 years in order to better understand the long-term effects of Tecartus.

Do not donate blood, organs, tissues, or cells for transplants.

Children, adolescents and young adults

Tecartus must not be used in children and adolescents below 18 years of age or young adults below 26 years of age.

Other medicines and Tecartus

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.

Before you are given Tecartus tell your doctor or nurse if you are taking any medicines that weaken your immune system such as corticosteroids, since these medicines may interfere with the effect of Tecartus.

In particular, you must not be given certain vaccines called live vaccines:
- In the 6 weeks before you are given the short course of lymphodepleting chemotherapy to prepare your body for the Tecartus cells.
- During Tecartus treatment.
- After treatment while the immune system is recovering.

Talk to your doctor if you need to have any vaccinations.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before being given this medicine. This is because the effects of Tecartus in pregnant or breast-feeding women are not known, and it may harm your unborn baby or your breast-fed child.
- If you are pregnant or think you may be pregnant after treatment with Tecartus, talk to your doctor immediately.
- You will be given a pregnancy test before treatment starts. Tecartus can only be given if the results show you are not pregnant.

Discuss pregnancy with your doctor if you have received Tecartus.

Driving and using machines

Tecartus can cause problems such as altered or decreased consciousness, confusion and seizures (fits) in the 8 weeks after it is given.

Do not drive, use machines, or take part in activities that need you to be alert for at least 8 weeks after your Tecartus treatment or until your doctor tells you that you have completely recovered.

Tecartus contains sodium, dimethylsulfoxide (DMSO) and gentamicin

This medicine contains 300 mg sodium (main component of cooking/table salt) in each infusion bag. This is equivalent to 15% of the recommended maximum daily dietary intake of sodium for an adult. It also contains DMSO and gentamicin which may cause severe hypersensitivity reactions.

3. How Tecartus is given

Tecartus will always be given to you by a healthcare professional.

- Since Tecartus is made from your own white blood cells, your cells will be collected from you to prepare your medicine. Your doctor will take some of your blood using a catheter placed in

your vein (a procedure call *leukapheresis*). Some of your white blood cells are separated from your blood and the rest of your blood is returned to your vein. This can take 3 to 6 hours and may need to be repeated.
- Your white blood cells are sent away to a manufacturing center to make your Tecartus. It usually takes about 2 to 3 weeks to make Tecartus but the time may vary.

Medicines given before Tecartus treatment

A few days before you receive Tecartus, you will be given lymphodepleting chemotherapy, which will allow the modified white blood cells in Tecartus to multiply in your body when the medicine is given to you.

During the 30 to 60 minutes before you are given Tecartus you may be given other medicines. This is to help prevent infusion reactions and fever. These other medicines may include:
- Paracetamol.
- An antihistamine such as diphenhydramine.

How you are given Tecartus

Tecartus will always be given to you by a doctor in a qualified treatment centre.

- Tecartus is given in a single dose.
- Your doctor or nurse will give you a single infusion of Tecartus through a catheter placed into your vein (*intravenous infusion*) over about 30 minutes.
- Tecartus is the genetically modified version of your white blood cells. Your healthcare professional handling the treatment will therefore take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases and will follow local guidelines on handling of waste of human-derived material to clean up or dispose of any material that has been in contact with it.

After you are given Tecartus

- You must stay within proximity of a hospital as discussed with your doctor for at least 4 weeks after you have been given Tecartus. Your doctor will recommend that you return to the hospital daily for at least 7 days or that you stay at the hospital as an in-patient for the first 7 days after Tecartus treatment. This is so your doctor can check if your treatment is working and help you if you have any side effects.

If you miss any appointments, call your doctor or your treatment centre as soon as possible to reschedule your appointment.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Do not try to treat your side effects on your own.

Tecartus can cause side effects that may be serious or life-threatening. **Get urgent medical attention** if you get any of the following side effects after the Tecartus infusion.

Very common: may affect more than 1 in 10 people

– Fever, chills, reduced blood pressure which may cause symptoms such as dizziness, lightheadedness, fluid in the lungs, which may be severe and can be fatal (all symptoms of a condition called *cytokine release syndrome*).

– Loss of consciousness or decreased level of consciousness, confusion or memory loss due to disturbances of brain function, difficulty speaking or slurred speech, involuntary shaking (*tremor*), sudden confusion with agitation, disorientation, hallucination or irritability (*delirium*).
– Fever, chills, which may be signs of an infection.

Other serious side effects which require immediate medical care are:

Common: may affect up to 1 in 10 people

– Fits (seizures, including epileptic seizure, or series of seizures, lasting longer than 5 minutes).

Other possible side effects

Other side effects are listed below. If these side effects become severe or serious, tell your doctor immediately.

Very common: may affect more than 1 in 10 people

– Abnormally low number of white blood cells, which may increase your risk of infection.
– Low number of cells that help clot the blood *(thrombocytopenia)*: symptoms can include excessive or prolonged bleeding or bruising.
– High blood pressure.
– Decrease in the number of red blood cells (cells that carry oxygen): symptoms can include extreme tiredness with a loss of energy.
– Extreme tiredness.
– Fast or slow heartbeat.
– Decrease of oxygen reaching body tissues: symptoms can include changes to the colour of your skin, confusion, rapid breathing.
– Shortness of breath, cough.
– Excessive bleeding.
– Nausea, constipation, diarrhoea, abdominal pain, vomiting.
– Muscle pain, joint pain, bone pain, pain in the extremities of the body.
– Lack of energy or strength, muscular weakness, difficulty moving, muscle spasm.
– Headache.
– Kidney problems causing your body to hold onto fluid, build-up of fluids in tissue *(oedema)* which can lead to weight gain and difficulty in breathing.
– High levels of uric acid and sugar *(glucose)*seen in blood tests.
– Low levels of sodium, magnesium, phosphate, potassium or calcium seen in blood tests.
– Decreased appetite, sore mouth.
– Difficulty sleeping, anxiety.
– Swelling in the limbs, fluid around the lungs *(pleural effusion)*.
– Skin rash or skin problems.
– Low levels of immunoglobulins seen in blood test, which may lead to infections.
– Increase in liver enzymes seen in blood tests.
– Nerve pain.

Common: may affect up to 1 in 10 people

– Low levels of albumin seen in blood tests.
– High levels of bilirubin seen in blood tests.
– Irregular heartbeat *(arrhythmia)*.
– Loss of control of body movements.
– Dry mouth, dehydration, difficulty swallowing.
– Decreased output of urine (due to kidney problems described above).
– Breathlessness *(respiratory failure)*.
– Difficulty breathing which makes you unable to speak in full sentence, cough due to fluid in the lungs.

- Increase of the pressure inside your skull.
- Blood clots: symptoms can include pain in the chest or upper back, difficulty breathing, coughing up blood or cramping pain, swelling in a single leg, warm and darkened skin around the painful area.
- Alteration of the blood ability to form clots (*coagulopathy*): symptoms can include excessive or prolonged bleeding or bruising.
- Changes in vision which makes it difficult to see things *(visual impairment).*
- Infusion related reactions: symptoms including dizziness or fainting, flushing, rash, itching, fever, shortness of breath or vomiting, abdominal pain, and diarrhoea.
- Hypersensitivity: symptoms such as rash, hives, itching, swelling and anaphylaxis.

A new type of cancer beginning in a type of white blood cells called T-cells (secondary malignancy of T-cell origin) has been reported for other similar medicines.

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Tecartus

The following information is intended for doctors only.

Do not use this medicine after the expiry date which is stated on the container label and infusion bag after EXP.

Store frozen in vapour phase of liquid nitrogen ≤ − 150 °C until thawed for use.

Tecartus may be stored a single time at -80 °C (± 10 °C), for up to 90 days. After storage at -80 °C (± 10 °C), use the product within the 90-day period or the expiry date, whichever comes first. After these dates the product must be discarded.

Do not refreeze.

6. Contents of the pack and other information

What Tecartus contains

The active substance is brexucabtagene autoleucel ($0.4 – 2 \times 10^8$ cells dispersion for infusion). Each patient-specific single infusion bag contains a dispersion 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 for mantle cell lymphoma patients and a target dose of 1×10^6 anti-CD19 CAR-positive viable T cells/kg for B-cell acute lymphoblastic leukaemia patients.
The other ingredients (excipients) are: Cryostor CS10 (contains DMSO), sodium chloride, human albumin. See section 2 “Tecartus contains sodium, dimethyl sulphoxide (DMSO), and residual gentamicin”.

This medicine contains genetically modified human blood cells.

What Tecartus looks like and contents of the pack

Tecartus is a clear to opaque, white to red dispersion for infusion, supplied in an infusion bag individually packed in a metal cassette. A single infusion bag contains approximately 68 mL of cell dispersion.

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Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

Manufacturer
Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

This medicine has been given ‘conditional approval’.
This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

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The following information is intended for healthcare professionals only:

It is important that you read the entire content of this procedure prior to administering Tecartus.

Precautions to be taken before handling or administering 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.

Work surfaces and materials that have potentially been in contact with Tecartus must be decontaminated according to local guidelines on the handling of waste of human-derived materials.

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's 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 (or 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, the infusion must begin within 30 minutes of thaw completion.

Do NOT use a leukodepleting filter.

Administration

- The medicine must be administered in a qualified treatment centre by a physician(s) with experience in the treatment of haematological malignancies and trained for administration and management of patients treated with Tecartus.
- Ensure that at least 1 dose of tocilizumab per patient and emergency equipment are available prior to infusion and during the recovery period. Hospitals and associated centres should have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensure that suitable alternative measures to treat CRS instead of tocilizumab are available on-site.
- The patient's identity must be matched with the patient identifiers on the infusion bag.
- Tecartus is for autologous use only.
- Tecartus must be administered as an intravenous infusion using latex-free intravenous tubing without a leukocyte depleting filter within 30 minutes by either gravity or a peristaltic pump.
- Gently agitate the infusion bag during infusion to prevent cell clumping. All contents of the infusion bag must be infused.
- Sterile sodium chloride 9 mg/mL (0.9%) (0.154 mmol sodium per mL) solution for injection must be used to prime the tubing prior to infusion as well as rinse it afterwards. When the full volume of Tecartus has been infused, the infusion bag must be rinsed with 10 to 30 mL sodium chloride 9 mg/mL (0.9%) solution for injection by back priming to ensure as many cells as possible are infused into the patient.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and any waste 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 handling of waste of human-derived material.

Accidental exposure

In case of accidental exposure, local guidelines on handling of human-derived material must be followed which may include washing of the contaminated skin, removal of contaminated clothes. Work surfaces and material which have potentially been in contact with Tecartus must be decontaminated with appropriate disinfectant.