1. NAME OF THE MEDICINAL PRODUCT

Kymriah 1.2 x 10^6 – 6 x 10^8 cells dispersion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Kymriah is an immunocellular therapy containing tisagenlecleucel, autologous T cells genetically modified *ex vivo* using a lentiviral vector encoding an anti-CD19 chimeric antigen receptor (CAR).

2.2 Qualitative and quantitative composition

Each ethylene vinyl acetate (EVA) infusion bag of Kymriah contains tisagenlecleucel cell dispersion at a batch-dependent concentration of autologous T cells genetically modified to express an anti-CD19 chimeric antigen receptor (CAR-positive viable T cells) (see section 4.2).

The concentration of CAR-positive viable T cells is dependent on indication and patient body weight (for B-cell acute lymphoblastic leukaemia [ALL]). The cellular composition and the final cell number varies between individual patient batches. In addition to T cells, NK cells may be present. The quantitative information regarding CAR-positive viable T cells/mL and total cells in the product is presented in the batch-specific documentation accompanying Kymriah.

1-3 infusion bags containing a total of 1.2 x 10^6 to 6 x 10^8 CAR-positive viable T cells.

Excipient with known effect

This medicinal product contains 2.43 mg sodium per mL and 24.3 to 121.5 mg sodium per dose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for infusion.

A colourless to slightly yellow dispersion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kymriah is indicated for the treatment of:

- Paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.
- Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

4.2 Posology and method of administration

Kymriah must be administered in a qualified treatment centre. Therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of haematological malignancies and trained for administration and management of patients treated with Kymriah. A minimum of four doses of tocilizumab for use in the event of cytokine release syndrome and emergency equipment must be available prior to infusion.

Kymriah is intended for autologous use only (see section 4.4). Manufacture and release of Kymriah usually takes about 3-4 weeks.

Posology

Dosage in paediatric and young adult B-cell ALL patients

- For patients 50 kg and below: 0.2 to 5 x 10^6 CAR-positive viable T cells/kg body weight.
- For patients above 50 kg: 0.1 to 2.5 x 10^8 CAR-positive viable T cells (non-weight based).

Dosage in adult DLBCL patients

- 0.6 to 6 x 10^8 CAR-positive viable T cells (non-weight based).

Pre-treatment conditioning (lymphodepleting chemotherapy)

Lymphodepleting chemotherapy is recommended to be administered before Kymriah infusion unless the white blood cell (WBC) count within one week prior to infusion is ≤1,000 cells/μL.

Kymriah is recommended to be infused 2 to 14 days after completion of the lymphodepleting chemotherapy. The availability of Kymriah must be confirmed prior to starting the lymphodepleting regimen. If there is a delay of more than 4 weeks between completing lymphodepleting chemotherapy and the infusion and the WBC count is >1,000 cells/μL, then the patient should be re-treated with lymphodepleting chemotherapy prior to receiving Kymriah.

B-cell ALL

The recommended lymphodepleting chemotherapy regimen is:

- Fludarabine (30 mg/m^2 intravenous daily for 4 days) and cyclophosphamide (500 mg/m^2 intravenous daily for 2 days starting with the first dose of fludarabine).

If the patient experienced a previous Grade 4 haemorrhagic cystitis with cyclophosphamide, or demonstrated a chemorefractory state to a cyclophosphamide-containing regimen administered shortly before lymphodepleting chemotherapy, then the following should be used:

- Cytarabine (500 mg/m^2 intravenous daily for 2 days) and etoposide (150 mg/m^2 intravenous daily for 3 days starting with the first dose of cytarabine).

DLBCL
The recommended lymphodepleting chemotherapy regimen is:
- Fludarabine (25 mg/m^2 intravenous daily for 3 days) and cyclophosphamide (250 mg/m^2 intravenous daily for 3 days starting with the first dose of fludarabine).

If the patient experienced a previous Grade 4 haemorrhagic cystitis with cyclophosphamide, or demonstrated a chemorefractory state to a cyclophosphamide-containing regimen administered shortly before lymphodepleting chemotherapy, then the following should be used:
- Bendamustine (90 mg/m^2 intravenous daily for 2 days).

Lymphodepleting chemotherapy may be omitted if a patient's white blood cell (WBC) count is ≤1,000 cells/μL within 1 week prior to Kymriah infusion.

Pre-medication
To minimise potential acute infusion reactions, it is recommended that patients be pre-medicated with paracetamol and diphenhydramine or another H1 antihistamine within approximately 30 to 60 minutes prior to Kymriah infusion. Corticosteroids should not be used at any time except in the case of a life-threatening emergency (see section 4.4).

Clinical assessment prior to infusion

Kymriah treatment should be delayed in some patient groups at risk (see section 4.4).

Monitoring after infusion
- Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential cytokine release syndrome, neurological events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs/symptoms of cytokine release syndrome and/or neurological events.
- After the first 10 days following the infusion, the patient should be monitored at the physician's discretion.
- Patients should be instructed to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion.

Special populations

Paediatric population
B-cell ALL: No formal studies have been performed in paediatric patients below 3 years of age.
DLBCL: The safety and efficacy of Kymriah in children and adolescents below 18 years of age have not yet been established. No data are available.

Elderly
B-cell ALL: The safety and efficacy of Kymriah in this population have not been established.
DLBCL: No dose adjustment is required in patients over 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 Kymriah for patients with a positive test for active HBV, HCV or HIV. Therefore, leukapheresis material from these patients will not be accepted for Kymriah manufacturing.

Method of administration

Kymriah is for intravenous use only.

Precautions to be taken before handling or administering the medicinal product
This medicinal product contains genetically modified human blood cells. Healthcare professionals handling Kymriah should therefore take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases.

Preparation for infusion
Prior to Kymriah infusion, it must be confirmed that the patient's identity matches the essential unique patient information on the infusion bag(s).

The timing of thaw of Kymriah and infusion should be coordinated. Please refer to section 6.6 for details on inspection and thawing of the infusion bag. The infusion start time should be confirmed in advance and adjusted for thaw so that Kymriah is available for infusion when the recipient is ready. Once Kymriah has been thawed and is at room temperature (20°C -25°C), it should be infused within 30 minutes to maintain maximum product viability, including any interruption during the infusion.

Administration
Kymriah should be administered as an intravenous infusion through latex-free intravenous tubing without a leukocyte depleting filter, at approximately 10 to 20 mL per minute by gravity flow. All contents of the infusion bag(s) should be infused. Sodium chloride 9 mg/mL (0.9%) solution for injection should be used to prime the tubing prior to infusion and to rinse it after infusion. When the full volume of Kymriah has been infused, the infusion bag should 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.

For special precautions for disposal 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

Reasons to delay treatment

Due to the risks associated with Kymriah treatment, infusion should be delayed if a patient has any of the following conditions:
- Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions or hypotension) from preceding chemotherapies.
- Active uncontrolled infection.
- Active graft-versus-host disease (GVHD).
- Significant clinical worsening of leukaemia burden or lymphoma following lymphodepleting chemotherapy.

Blood, organ, tissue and cell donation

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

Active central nervous system (CNS) leukaemia or lymphoma

There is limited experience of use of Kymriah in patients with active CNS leukaemia and active CNS lymphoma. Therefore the risk/benefit of Kymriah has not been established in these populations.

Cytokine release syndrome

Cytokine release syndrome, including fatal or life-threatening events, has been frequently observed after Kymriah infusion (see section 4.8). In almost all cases, development of cytokine release syndrome occurred between 1 to 10 days (median onset 3 days) after Kymriah infusion. The median time to resolution of cytokine release syndrome was 7 days.

Symptoms of cytokine release syndrome may include high fever, rigors, myalgia, arthralgia, nausea, vomiting, diarrhoea, diaphoresis, rash, anorexia, fatigue, headache, hypotension, encephalopathy, dyspnoea, tachypnoea, and hypoxia. Additional organ system adverse reactions, including transient cardiac insufficiency and arrhythmia, renal insufficiency, elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT) and elevated bilirubin have been observed. In some cases, disseminated intravascular coagulation (DIC), with low fibrinogen levels, capillary leak syndrome (CLS), and haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) have been reported in the setting of cytokine release syndrome. Patients should be closely monitored for signs or symptoms of these events, including fever.

Risk factors for severe cytokine release syndrome in paediatric and young adult B-cell ALL patients are: high pre-infusion tumour burden, uncontrolled or accelerating tumour burden following lymphodepleting chemotherapy, active infection and early onset of fever or cytokine release syndrome following Kymriah infusion. Risk factors for developing severe cytokine release syndrome in adult DLBCL patients are not known.

In all indications, appropriate prophylactic and therapeutic treatment for infections should be provided, and complete resolution of any existing infections should be ensured. Infections may also occur during cytokine release syndrome and may increase the risk of a fatal event.

Management of cytokine release syndrome associated with Kymriah

Cytokine release syndrome is managed solely based on clinical presentation and according to the cytokine release syndrome management algorithm provided in Table 1. Anti-IL-6 based therapy such as tocilizumab has been administered for moderate or severe cytokine release syndrome associated with Kymriah and a minimum of four doses of tocilizumab must be on site and available for administration prior to Kymriah infusion. Corticosteroids may be administered in cases of life-threatening emergencies. Tisagenlecleucel continues to expand and persist following administration of tocilizumab and corticosteroids. Patients with medically significant cardiac dysfunction should be managed by standards of critical care and measures such as echocardiography should be considered. Tumour necrosis factor (TNF) antagonists are not recommended for management of Kymriah-associated cytokine release syndrome.

Table 1 Cytokine release syndrome management algorithm

Cytokine release syndrome severity	**Management**
Prodromal syndrome: Low-grade fever, fatigue, anorexia	Observe in person; exclude infection; administer antibiotics per local guidelines if neutropenic; provide symptomatic support.
Cytokine release syndrome requiring mild intervention - one or more of the following: – High fever – Hypoxia – Mild hypotension	Administer antipyretics, oxygen, intravenous fluids and/or low-dose vasopressors as needed.
Cytokine release syndrome requiring moderate to aggressive intervention - one or more of the following: – Haemodynamic instability despite intravenous fluids and vasopressor support – Worsening respiratory distress, including pulmonary infiltrates, increasing oxygen requirement including high-flow oxygen and/or need for mechanical ventilation – Rapid clinical deterioration	• Administer high-dose or multiple vasopressors, oxygen, mechanical ventilation and/or other supportive care as needed. • Administer tocilizumab. - Patient weight less than 30 kg: 12 mg/kg intravenously over 1 hour - Patient weight ≥30 kg: 8 mg/kg intravenously over 1 hour (maximum dose 800 mg) Repeat tocilizumab as needed at a minimum interval of 8 hours if there is no clinical improvement. If no response to second dose of tocilizumab, consider a third dose of tocilizumab or pursue alternative measures for treatment of cytokine release syndrome. Limit to a maximum total of 4 tocilizumab doses. • If no clinical improvement within 12 to 18 hours of the first tocilizumab dose, or worsening at any time, administer methylprednisolone 2 mg/kg as an initial dose, then 2 mg/kg per day until vasopressors and high-flow oxygen are no longer needed, then taper.

Neurological adverse reactions

Neurological events, in particular encephalopathy, confusional state or delirium, occur frequently with Kymriah and can be severe or life-threatening (see section 4.8). Other manifestations included seizures, aphasia and speech disorder. The majority of neurological events occurred within 8 weeks following Kymriah infusion and were transient. The median time to onset of neurological events was 7 days in B-cell ALL and DLBCL. The median time to resolution was 7 days for B-cell ALL and 12 days for DLBCL. Neurological events can be concurrent with cytokine release syndrome, following resolution of cytokine release syndrome or in the absence of cytokine release syndrome.

Patients should be monitored for neurological events. In case of neurological events, patients should be diagnostically worked up and managed depending on the underlying pathophysiology and in accordance with local standard of care.

Infections and febrile neutropenia

Patients with active, uncontrolled infection should not start Kymriah treatment until the infection is resolved. Prior to Kymriah infusion, infection prophylaxis should follow standard guidelines based on the degree of preceding immunosuppression.

Serious infections, including life-threatening or fatal infections, occurred frequently in patients after Kymriah infusion (see section 4.8). Patients should be monitored for signs and symptoms of infection and treated appropriately. As appropriate, prophylactic antibiotics should be administered and surveillance testing should be employed prior to and during treatment with Kymriah. Infections are known to complicate the course and management of concurrent cytokine release syndrome.

Febrile neutropenia was frequently observed in patients after Kymriah infusion (see section 4.8) and may be concurrent with cytokine release syndrome. In the event of febrile neutropenia, infection should be evaluated and managed appropriately with broad-spectrum antibiotics, fluids and other supportive care, as medically indicated.

In patients achieving complete remission following Kymriah, resulting low immunoglobulin levels can increase the risk for infections. Attention to signs and symptoms of infection should be implemented according to age and standard specific guidelines.

Prolonged cytopenias

Patients may continue to exhibit cytopenias for several weeks following Kymriah infusion and should be managed according to standard guidelines. The majority of patients who had cytopenias at day 28 following Kymriah treatment resolved to Grade 2 or below within three months after treatment. Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, particularly granulocyte macrophage-colony stimulating factor (GM-CSF), have the potential to worsen cytokine release syndrome symptoms and are not recommended during the first 3 weeks after Kymriah infusion or until cytokine release syndrome has resolved.

Secondary malignancies

Patients treated with Kymriah may develop secondary malignancies or recurrence of their cancer. They should be monitored life-long for secondary malignancies. In the event that a secondary malignancy occurs, the company should be contacted to obtain instructions on patient samples to collect for testing.

Hypogammaglobulinaemia

Hypogammaglobulinaemia and agammaglobulinaemia can occur in patients with a complete remission after Kymriah infusion. Immunoglobulin levels should be monitored after treatment with Kymriah. In patients with low immunoglobulin levels pre-emptive measures such as infection precautions, antibiotic prophylaxis and immunoglobulin replacement should be taken according to age and standard guidelines.

Live vaccines

The safety of immunisation with live viral vaccines during or following Kymriah treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Kymriah treatment, and until immune recovery following treatment with Kymriah (see section 4.5).

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 Kymriah infusion. Signs and symptoms of TLS should be monitored and events managed according to standard guidelines.

Concomitant disease

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

Prior bone marrow transplant

It is not recommended that patients receive Kymriah within 4 months of undergoing an allogeneic stem cell transplant (SCT) because of the potential risk of Kymriah worsening GVHD. Leukapheresis for Kymriah manufacturing should be performed at least 12 weeks after allogeneic SCT.

HBV reactivation

HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with medicinal products directed against B cells.

There is currently no experience with manufacturing Kymriah for patients testing positive for HBV, HCV and HIV.

Screening for HBV, HCV and HIV must be performed in accordance with clinical guidelines before collection of cells for manufacturing.

Prior treatment with anti-CD19 therapy

There is limited experience with Kymriah in patients exposed to prior CD19-directed therapy. Kymriah is not recommended if the patient has relapsed with CD19-negative leukaemia after prior anti-CD19 therapy.

Interference with serological testing

Due to limited short spans of identical genetic information between the lentiviral vector used to create Kymriah and HIV, some commercial HIV nucleic acid tests (NAT) may give a false positive result.

Sodium and potassium content

This medicinal product contains 24.3 to 121.5 mg sodium per dose, equivalent to 1 to 6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicinal product contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially "potassium-free".

Content of dextran 40 and dimethyl sulfoxide (DMSO)

This medicinal product contains 11 mg dextran 40 and 82.5 mg dimethyl sulfoxide (DMSO) per mL. Each of these excipients are known to possibly cause anaphylactic reaction following parenteral administration. Patients not previously exposed to dextran and DMSO should be observed closely during the first minutes of the infusion period.

4.5 Interaction with other medicinal products and other forms of interaction

No pharmacokinetic or pharmacodynamic drug interaction studies with tisagenlecleucel have been performed. The co-administration of agents known to inhibit T-cell function has not been formally studied. Administration of low-dose steroids as per the cytokine release syndrome treatment algorithm does not impact the expansion and persistence of CAR-T cells. The co-administration of agents known to stimulate T-cell function has not been investigated and the effects are unknown.

Live vaccines

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Pregnancy status for females of child-bearing age should be verified prior to starting treatment with Kymriah.

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 Kymriah.

Pregnancy

There are no data from the use of Kymriah in pregnant women. No animal studies have been conducted with Kymriah to assess whether it can cause foetal harm when administered to a pregnant woman (see section 5.3). It is not known whether Kymriah has the potential to be transferred to the foetus via the placenta and could cause foetal toxicity, including B-cell lymphocytopenia. Kymriah is not recommended during pregnancy and in women of childbearing potential not using contraception.

Pregnant women should be advised on the potential risks to the foetus. Pregnancy after Kymriah therapy should be discussed with the treating physician. Pregnant women who have received Kymriah may have hypogammaglobulinaemia. Assessment of immunoglobulin levels is indicated in newborns of mothers treated with Kymriah.

Breast-feeding

It is unknown whether Kymriah cells are excreted in human milk. A risk to the breast-fed infant cannot be excluded. Women who are breast-feeding should be advised of the potential risk to the breast-fed infant.

Following administration of Kymriah, breast-feeding should be discussed with the treating physician.

Fertility

There are no data on the effect of Kymriah on fertility. Effects of Kymriah on male and female fertility have not been evaluated in animal studies.

4.7 Effects on ability to drive and use machines

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

Due to the potential for neurological events, including altered mental status or seizures, patients receiving Kymriah are at risk for altered or decreased consciousness or coordination in the 8 weeks following infusion.

4.8 Undesirable effects

Summary of the safety profile

B-cell ALL
The most common non-haematological adverse reactions were cytokine release syndrome (77%), infections (65%), hypogammaglobulinaemia (47%), pyrexia (40%) and decreased appetite (39%).

Grade 3 and 4 adverse reactions were reported in 88% of patients. The most common Grade 3 and 4 non-haematological adverse reaction was cytokine release syndrome (47%).

The most common Grade 3 and 4 haematological laboratory abnormalities were white blood cells decreased (99%), neutrophils decreased (95%), lymphocytes decreased (95%), platelets decreased (77%) and haemoglobin decreased (53%).

Grade 3 and 4 adverse reactions were more often observed within the initial 8 weeks post-infusion (83% of patients) compared to after 8 weeks post-infusion (46% of patients).

DLBCL
The adverse reactions described in this section were identified in 111 patients infused with Kymriah in one global multicentre international study, i.e. the ongoing pivotal clinical study CCTL019C2201.

The most common non-haematological adverse reactions were cytokine release syndrome (58%), infections (54%), pyrexia (35%), diarrhoea (32%), nausea (29%), hypotension (26%) and fatigue (26%).

Grade 3 and 4 adverse reactions were reported in 89% of patients. The most common Grade 3 and 4 non-haematological adverse reactions were infections (32%) and cytokine release syndrome (22%).

The most common (>25%) Grade 3 and 4 haematological laboratory abnormalities were lymphocyte count decreased (95%), neutrophil count decreased (81%), white blood cell count decreased (77%), haemoglobin decreased (59%) and platelet count decreased (55%).

Grade 3 and 4 adverse reactions were more often observed within the initial 8 weeks post-infusion (85%) compared to after 8 weeks post-infusion (49%).

Tabulated list of adverse drug reactions

The adverse reactions described in this section were identified in 75 and 111 patients in the ongoing multicentre pivotal clinical studies (CCTL019B2202 and CCTL019C2201). Adverse drug reactions from these clinical studies (Table 2) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

Table 2 Adverse drug reactions observed in clinical studies

Adverse drug reaction (MedDRA system organ class)	**Studies B2202 (N=75) + C2201 (N=111)**	
	Very common (≥1/10)	**Common (≥1/100 to <1/10)**
Infections and infestations[a)]	Infections - pathogen unspecified Viral infections Bacterial infections Fungal infections	
Blood and lymphatic system disorders	Febrile neutropenia Leukopenia Lymphopenia Anaemia Thrombocytopenia	Disseminated intravascular coagulation Coagulopathy Histiocytosis haematophagic Pancytopenia
Immune system disorders	Cytokine release syndrome Hypogammaglobulinaemia[b)]	Graft-versus-host disease
Metabolism and nutrition disorders	Decreased appetite Hypokalaemia Hypophosphataemia Hypocalcaemia Hypomagnesaemia Hypoalbuminaemia Hyperuricaemia Hyperglycaemia	Fluid overload Hypermagnesaemia Hyponatraemia Hyperphosphataemia Tumour lysis syndrome
Psychiatric disorders	Delirium[c)] Anxiety Sleep disorder[d)]	
Nervous system disorders	Headache[e)] Encephalopathy[f)] Dizziness	Tremor Peripheral neuropathy[g)] Speech disorders[h)] Seizure[i)] Cerebral haemorrhage** Neuralgia Ischaemic cerebral infarction
Cardiac disorders	Tachycardia[j)]	Cardiac failure[k)] Arrhythmia[l)] Cardiac arrest

Vascular disorders	Hypotension Hypertension	Capillary leak syndrome Flushing
Respiratory, thoracic and mediastinal disorders	Cough[m)] Hypoxia Dyspnoea[n)] Pulmonary oedema Pleural effusion Tachypnoea	Epistaxis Lung infiltration
Gastrointestinal disorders	Diarrhoea Nausea Vomiting Constipation Abdominal pain[o)]	Dry mouth Mouth haemorrhage Stomatitis Abdominal distension Ascites Abdominal compartment syndrome
Hepatobiliary disorders		Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	Rash[p)]	Pruritus Erythema Night sweats Petechiae Hyperhidrosis
Musculoskeletal and connective tissue disorders	Back pain Myalgia Arthralgia	
Renal and urinary disorders	Acute kidney injury[q)]	
General disorders and administration site conditions	Pyrexia Fatigue Oedema[r)] Pain[s)] Chills	Asthenia Influenza-like illness Multiple organ dysfunction syndrome
Investigations	Haemoglobin decreased* Lymphocyte count decreased* White blood cell count decreased* Neutrophil count decreased* Platelet count decreased* Aspartate aminotransferase increased Alanine aminotransferase increased Blood bilirubin increased International normalised ratio increased Weight decreased	Activated partial thromboplastin time prolonged Blood fibrinogen decreased Serum ferritin increased Blood alkaline phosphatase increased Fibrin D dimer increased Prothrombin time prolonged

a) Infections and infestations presented reflect high-level group terms.

b) Hypogammaglobulinaemia includes immunoglobulins decreased, blood immunoglobulin A decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, immunodeficiency common variable and hypogammaglobulinaemia.

c) Delirium includes agitation, delirium, hallucination, hallucination visual, irritability and restlessness.

d) Sleep disorder includes sleep disorder, insomnia and nightmare.

e) Headache includes headache and migraine.

f) Encephalopathy includes depressed level of consciousness, mental status changes, automatism, cognitive disorder, confusional state, disturbance in attention, encephalopathy, posterior reversible encephalopathy syndrome, somnolence, lethargy, memory impairment, metabolic encephalopathy and thinking abnormal.

g) Peripheral neuropathy includes paraesthesia, peripheral sensory neuropathy, neuropathy peripheral, hyperaesthesia and hypoaesthesia.

h)	Speech disorders includes speech disorders, dysarthria and aphasia.
i)	Seizure includes seizure, generalised tonic-clonic seizures and status epilepticus.
j)	Tachycardia includes sinus tachycardia and tachycardia.
k)	Cardiac failure includes cardiac failure, left ventricular dysfunction, cardiac failure congestive and right ventricular dysfunction.
l)	Arrhythmia includes atrial fibrillation and supraventricular tachycardia.
m)	Cough includes cough, productive cough and upper-airway cough syndrome.
n)	Dyspnoea includes dyspnoea, dyspnoea exertional, respiratory distress and respiratory failure.
o)	Abdominal pain includes abdominal pain, abdominal pain upper and abdominal discomfort.
p)	Rash includes rash, rash maculo-papular, rash papular and rash pruritic.
q)	Acute kidney injury includes acute kidney injury, anuria, azotaemia, blood creatinine increased, renal failure, renal tubular dysfunction and renal tubular necrosis.
r)	Oedema includes oedema peripheral, generalised oedema, localised oedema and face oedema.
s)	Pain includes pain and pain in extremity.
*	Frequency is based on laboratory values. Patients are counted only for the worst grade observed post baseline.
**	With reported sequelae of secondary cerebral oedema.

Description of selected adverse drug reactions

Cytokine release syndrome

In the ongoing clinical studies in paediatric and young adult B-cell ALL (N=75), cytokine release syndrome was reported in 77% of patients (47% with Grade 3 or 4). Two deaths occurred within 30 days of Kymriah infusion: one patient died with cytokine release syndrome and progressive leukaemia and the second patient had resolving cytokine release syndrome with abdominal compartment syndrome, coagulopathy and renal failure when death occurred due to an intracranial haemorrhage.

In the ongoing clinical study in DLBCL (N=111), cytokine release syndrome was reported in 58% of patients, (22% with Grade 3 or 4).

Cytokine release syndrome was graded with the Penn scale as follows: Grade 1: mild reactions, e.g. reactions requiring supportive care; Grade 2: moderate reactions, e.g. reactions requiring intravenous therapies; Grade 3: severe reactions, e.g. reactions requiring low-dose vasopressors or supplemental oxygen; Grade 4: life-threatening reactions, e.g. those requiring high-dose vasopressors or intubation; Grade 5: death.

For clinical management of cytokine release syndrome, see section 4.4 and Table 1.

Febrile neutropenia and infections

Severe febrile neutropenia (Grade 3 or 4) was observed in 36% of paediatric and young adult B-cell ALL patients and 15% of DLBCL patients. See section 4.4 for the management of febrile neutropenia before and after Kymriah infusion.

In B-cell ALL patients severe infections (Grade 3 and higher), which can be life-threatening or fatal, occurred in 44% of patients after Kymriah infusion. The overall incidence (all grades) was 65% (unspecified 49%, viral 32%, bacterial 24% and fungal 15%) (see section 4.4). 43% of the patients experienced an infection of any type within 8 weeks after Kymriah infusion.

In DLBCL patients severe infections (Grade 3 and higher), which can be life-threatening or fatal, occurred in 32% of patients. The overall incidence (all grades) was 54% (unspecified 44%, bacterial 10%, fungal 10% and viral 8%) (see section 4.4). 34% of the patients experienced an infection of any type within 8 weeks.

Prolonged cytopenias
Cytopenias are very common with Kymriah therapy.

In paediatric and young adult B-cell ALL patients, Grade 3 and 4 cytopenias not resolved by day 28 were reported based on laboratory findings and included leukopenia (55%), neutropenia (53%), lymphopenia (43%), thrombocytopenia (41%) and anaemia (12%).

In adult DLBCL, patients, Grade 3 and 4 cytopenias not resolved by day 28 were reported based on laboratory findings and included thrombocytopenia (41%), lymphopenia (28%), neutropenia (24%), leukopenia (21%) and anaemia (14%).

Neurological adverse reactions
The majority of neurological events occurred within 8 weeks following infusion and were transient.

In paediatric and young adult B-cell ALL patients, manifestations of encephalopathy and/or delirium occurred in 40% of patients (13% were Grade 3 or 4) within 8 weeks after Kymriah infusion. In DLBCL patients, manifestations of encephalopathy and/or delirium occurred in 21% of patients (12% were Grade 3 or 4) within 8 weeks after Kymriah infusion.

Hypogammaglobulinaemia
Hypogammaglobulinaemia was reported in 47% of patients treated with Kymriah for r/r ALL and 14% of patients with r/r DLBCL.

Pregnant women who have received Kymriah may have hypogammaglobulinaemia. Immunoglobulin levels should be assessed in newborns of mothers treated with Kymriah.

Immunogenicity

In clinical studies, humoral immunogenicity of tisagenlecleucel was measured by determination of anti-murine CAR19 antibodies (anti-mCAR19) in serum pre- and post-administration. The majority of patients tested positive for pre-dose anti-mCAR19 antibodies in paediatric and young adult ALL (B2202 and B2205J, 84.6%) and adult DLBCL (C2201, 91.4%).

Treatment-induced anti-mCAR19 antibodies were shown in 34.6% of paediatric and young adult ALL and 5% of adult DLBCL patients. Pre-existing and treatment-induced antibodies were not associated with an impact on clinical response nor did they have an impact on the expansion and persistence of tisagenlecleucel. There is no evidence that the presence of pre-existing and treatment-induced anti-mCAR19 antibodies impacts the safety or effectiveness of Kymriah.

T-cell immunogenicity responses were not observed in paediatric and young adult B-cell ALL and adult r/r DLBCL patients.

4.9 Overdose

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antineoplastic agents, ATC code: Not yet assigned

Mechanism of action

Tisagenlecleucel is an autologous, immunocellular cancer therapy which involves reprogramming a patient's own T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19 expressing cells. The CAR is comprised of a murine single chain antibody fragment which recognises CD19 and is fused to intracellular signalling domains from 4-1BB (CD137) and CD3 zeta. The CD3 zeta component is critical for initiating T-cell activation and antitumour activity, while 4-1BB enhances the expansion and persistence of tisagenlecleucel. Upon binding to CD19-expressing cells, the CAR transmits a signal promoting T-cell expansion and persistence of tisagenlecleucel.

Clinical efficacy and safety

Acute lymphoblastic leukaemia (ALL)
The safety and efficacy of Kymriah treatment in paediatric and young adult patients with relapsed or refractory (r/r) B-cell ALL were evaluated in one pivotal (B2202) and two supportive (B2205J and B2101J) open-label, single-arm studies (160 patients in total, up to 25 years of age). All patients had leukapheresis products collected and cryopreserved prior to or during study entry.

The pivotal study (B2202) is a multicentre, single-arm phase II study in paediatric and young adult patients with r/r B-cell acute lymphoblastic leukaemia. Of 92 patients enrolled, 75 received infusion with Kymriah; for 7 patients (8%) Kymriah could not be manufactured; reasons for discontinuation prior to Kymriah infusion included death (n=7; 8%) or adverse events (n=3; 3%) while awaiting Kymriah manufacturing in the clinical study.

Key baseline information for enrolled and infused patients is presented in Table 3. A total of 72 out of 75 patients who received Kymriah infusion also received lymphodepleting chemotherapy after enrolment and prior to infusion of a single dose of Kymriah (see section 4.2 for condition of lymphodepleting chemotherapy).

Table 3 Study B2202: Baseline information across the enrolled and the infused patient population

	Enrolled N=92 n (%)	**Infused N=75 n (%)**
Age (years)		
Mean (standard deviation)	12.0 (5.43)	12.0 (5.28)
Median (minimum – maximum)	11.0 (3 – 27)	11.0 (3 – 23)
Age category (years) - n (%)		
<10 years	39 (42.4)	31 (41.3)
≥10 years and <18 years	37 (40.2)	31 (41.3)
≥18 years	16 (17.4)	13 (17.3)
Sex - n (%)		
Male	52 (56.5)	43 (57.3)
Female	40 (43.5)	32 (42.7)
Disease status (%)		
Primary refractory[1]	8 (8.7)	6 (8.0)
Relapsed disease[2]	84 (91.3)	69 (92.0)
Prior stem-cell transplantation - n (%)		
0	37 (40.2)	29 (38.7)
1	48 (52.2)	40 (53.3)
2	7 (7.6)	6 (8.0)

[1]Primary refractory: Never had a morphologic complete remission (CR) prior to the study;
[2]Relapsed disease: Had at least one relapse prior to the study

Efficacy was established through the primary endpoint of overall remission rate (ORR) within 3 months post infusion, as determined by Independent Review Committee (IRC) assessment, duration of remission (DOR) and the proportion of patients who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) with minimal residual disease (MRD) <0.01% by flow cytometry (MRD-negative). ORR included CR and CRi. See Table 4 for efficacy results from this study. ORR was consistent across all subgroups. Seven patients who achieved CR/CRi after Kymriah infusion went to transplant while in remission. Kymriah was administered in a qualified Kymriah treatment centre in an inpatient and outpatient setting.

Health-related quality of life (HRQoL) was evaluated by PedsQL™ and EQ-5D questionnaires completed by patients aged 8 years and above (n=58). Among patients responding (n=48), the mean (SD) change from baseline in the PedsQL total score was 13.5 (13.5) at month 3, 16.9 (17.6) at month 6 and 27.2 (21.7) at month 12, and the mean (SD) change from baseline in the EQ-5D VAS score was 16.5 (17.5) at month 3, 15.9 (20.1) at month 6 and 24.7 (18.6) at month 12, indicating overall clinically meaningful improvement in HRQoL following Kymriah infusion.

Special populations
No differences in efficacy or safety were observed between different age subgroups.

Patients with active CNS leukaemia
Of four patients with active CNS leukaemia (i.e. CNS-3) included in study B2101J, three experienced cytokine release syndrome (Grade 2-4) and transient neurological abnormalities (Grade 1-3) that resolved within 1-3 months of infusion. One patient died due to disease progression and the remaining three patients achieved a CR or CRi and remain alive 1.5-2 years after infusion.

Table 4 Study B2202: Efficacy results in paediatric and young adult patients with relapsed/refractory B-cell acute lymphoblastic leukaemia (ALL)

Primary endpoint	**Enrolled patients N=92**	**Infused patients N=75**
Overall remission rate (ORR)[1,2], n (%) 95% CI	**61 (66.3)** (55.7, 75.8) p<0.0001	**61 (81.3)** (70.7, 89.4) p<0.0001
CR[3], n (%)	45 (48.9)	45 (60.0)
CRi[4], n (%)	16 (17.4)	16 (21.3)
Key secondary endpoint	**N=92**	**N=75**
CR or CRi with MRD negative bone marrow[5,6], n (%) 95% CI	61 (66.3) (55.7, 75.8) p<0.0001	61 (81.3) (70.7, 89.4) p<0.0001
Duration of remission (DOR)[7]	**N=61**	**N=61**
% event free probability at 6 months	79.5	79.5
Median (months) (95% CI)	Not reached (8.6, NE[9])	Not reached (8.6, NE)
Other secondary endpoint	**N=92**	**N=75**
Overall survival (OS)[8]		
% survival probability at 6 months	77.4	90.3
% survival probability at 12 months	70.3	76.4
Median (months) (95% CI)	19.4 (14.8, NE)	19.1 (15.2, NE)

1 Requires remission status to be maintained for at least 28 days without clinical evidence of relapse.
2 Nominal one-sided exact p-value based on H0: ORR ≤20% vs. Ha: ORR >20%
3 CR (complete remission) was defined as <5% of blasts in the bone marrow, circulating blasts in blood should be <1%, no evidence of extramedullary disease, and full recovery of peripheral blood counts (platelets >100,000/μL and absolute neutrophil counts [ANC] >1,000/μL) without blood transfusion.
4 CRi (complete remission with incomplete blood count recovery) was defined as <5% of blasts in the bone marrow, circulating blasts in blood should be <1%, no evidence of extramedullary disease, and without full recovery of peripheral blood counts with or without blood transfusion.
5 MRD (minimal residual disease) negative was defined as MRD by flow cytometry <0.01%.
6 Nominal one-sided exact p-value based on H0: Rate of MRD negative remission ≤15% vs. Ha: >15%.
7 DOR was defined as time since onset of CR or CRi to relapse or death due to underlying indication, whichever is earlier (N=61).
8 OS was defined as time from date of Kymriah infusion to the date of death due to any cause for infused patients and from time of date of enrolment to the date of death due to any cause for enrolled patients.
9 Not estimable

Diffuse large B-cell lymphoma (DLBCL)
The safety and efficacy of Kymriah treatment in adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) who received ≥2 lines of chemotherapy, including rituximab and anthracycline, or relapsed following autologous haematopoietic stem cell transplantation (HSCT), was evaluated in an open-label, pivotal, single-arm study. Patients with T-cell rich/histiocyte-rich large B-cell lymphoma (THRBCL), primary cutaneous large B-cell lymphoma, primary mediastinal B-cell lymphoma (PMBCL), EBV-positive DLBCL of the elderly, Richter's transformation, and Burkitt lymphoma were not enrolled in study C2201.

The pivotal study (C2201) is a multicentre, single-arm phase II study in adult patients with relapsed or refractory DLBCL. Of 165 patients enrolled, 111 patients received infusion with Kymriah (4 infusions were pending at the time of analysis); for 12 patients (7%) Kymriah could not be manufactured. Approximately 30% of patients discontinued the study prior to Kymriah administration. Reasons for discontinuation prior to Kymriah infusion included death (n=16; 10%), physician decision/primary disease progression (n=16; 10%), patient decision (n=3; 2%) or adverse events (n=2; 1%) while awaiting Kymriah manufacturing in the clinical study.

Key baseline information for enrolled and infused patients is presented in Table 5. All patients had leukapheresis starting material collected and cryopreserved prior to or during study entry. The majority of patients (101/111, 91%) received bridging therapy for disease stabilisation. The type and duration of bridging therapy was left to the discretion of the physician. 103/111 patients (93%) received lymphodepleting chemotherapy prior to Kymriah infusion. Kymriah was given as a single-dose (0.6-6.0 x 10^8 CAR-positive viable T cells) intravenous infusion in a qualified Kymriah treatment centre in an inpatient and outpatient setting.

Table 5 Study C2201: Baseline information across the enrolled and the infused patient populations

	Enrolled N=165 n (%)	**Infused N=111 n (%)**
Age (years)		
Mean (standard deviation)	56 (12.9)	54 (13.0)
Median (minimum – maximum)	59 (22 - 76)	56 (22 - 76)
Age category (years) - n (%)		
<65 years	118 (71.5)	86 (77.5)
≥65 years	47 (28.5)	25 (22.5)
Sex - n (%)		
Male	103 (62.4)	68 (61.3)
Female	62 (37.6)	43 (38.7)
Prior haematopoietic stem cell transplant (SCT) - n (%)		
No	93 (56.4)	57 (51.4)
Yes	72 (43.6)	54 (48.6)
Stage III/IV disease at study entry - n (%)		
No	36 (21.8)	27 (24.3)
Yes	129 (78.2)	84 (75.7)
Number of prior lines of antineoplastic therapy – n (%)		
1	6 (3.6)	5 (4.5)
2	72 (43.6)	49 (44.1)
3	51 (30.9)	34 (30.6)
≥4	36 (21.8)	23 (20.7)
Disease status (%)		
Refractory to last line of therapy	96 (58.2)	61 (55.0)
Relapse to last line of therapy	69 (41.8)	50 (45.0)

The efficacy of Kymriah was evaluated through the primary endpoint of best overall response rate (ORR), which includes complete response (CR) and partial response (PR) as determined by Independent Review Committee (IRC) assessment as well as secondary endpoints including duration of response (Table 6). ORR was consistent across subgroups.

Table 6 Study C2201: Efficacy results in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy

	Enrolled patients	**Infused patients**
Primary endpoint	**N=165**	**EAS[5] N=93[6]**
Overall response rate (ORR) (CR+PR)[1], n (%) 95% CI	**56 (33.9)** (26.8, 41.7)	**48 (51.6)** (41.0, 62.1)
CR, n (%)	40 (24.2)	37 (39.8)
PR, n (%)	16 (9.7)	11 (11.8)
Response at month 3	N=165	N=93
ORR (%)	39 (23.6)	35 (37.6)
CR (%)	33 (20.0)	30 (32.3)
Response at month 6	N=165	N=92
ORR (%)	34 (20.6)	30 (32.6)
CR (%)	30 (18.2)	27 (29.3)
Duration of response (DOR)[2]	**N=56**	**N=48**
Median (months) (95% CI)	Not reached (10.0, NE[4])	Not reached (10.0, NE[4])
% relapse free probability at 6 months	66.7	68.2
% relapse free probability at 12 months	63.7	65.1
Other secondary endpoints	**N=165**	**FAS[7] N=111**
Overall survival (OS)[3]		
% survival probability at 6 months	56.2	62.1
% survival probability at 12 months	40.2	49.0
Median (months) (95% CI)	8.2 (5.8, 11.7)	11.7 (6.6, NE)

1 ORR is the proportion of patients with best overall response (BOR) of CR or PR based on the Lugano response criteria (Cheson 2014); non-infused patients were assigned BOR=Unknown (i.e. non-responders).

2 DOR was defined as time from achievement of CR or PR, whichever occurs first, to relapse or death due to DLBCL.

3 OS was defined as time from date of Kymriah infusion to the date of death due to any cause on FAS (N=111) and time from date of enrolment to the date of death due to any cause for enrolled patients (N=165).

4 Not estimable.

5 Efficacy analysis set (EAS) includes patients infused with Kymriah at least 3 months prior to data cutoff date.

6 The primary endpoint was analysed on all patients whose Kymriah was manufactured at the Novartis US facility.

7 The full analysis set (FAS) includes all patients infused with Kymriah.

Special populations

There are not enough data to determine whether there are any differences in efficacy or safety between different age subgroups, although the clinical benefit and safety experience in elderly patients with DLBCL above the age of 65 years (23% of the study population) were comparable to the overall population.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Kymriah in one or more subsets of the paediatric population in the following conditions: a) treatment of B-cell lymphoblastic lymphoma, and b) treatment of mature B-cell neoplasms (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Following infusion of Kymriah into paediatric and young adult r/r B-cell ALL and r/r DLBCL patients, Kymriah typically exhibited an initial rapid expansion followed by a slower bi-exponential decline.

Cellular kinetics in paediatric and young adult B-cell ALL patients

A summary of cellular kinetic parameters of tisagenlecleucel in paediatric and young adult B-cell ALL patients is provided in Table 7 below. The maximal expansion (C_{max}) was approximately 2-fold higher in CR/CRi patients (n=79) compared with non-responding (NR) patients (n=10) as measured by qPCR.

Table 7 Cellular kinetic parameters of tisagenlecleucel in paediatric and young adult r/r B-cell ALL (Studies B2202 and B2205J)

Parameter	Summary statistics	Responding patients (CR/CRi) N=80	Non-responding patients (NR) N=11
C_{max} (copies/μg)	Geometric mean (CV%), n	32,700 (163.4), 79	19,500 (123.7), 10
T_{max}[‡] (day)	Median [min;max], n	9.83 [0.0111;27.8], 79	20.0 [0.0278;62.7], 10
$AUC_{0\text{-}28d}$ (copies/μg*day)	Geometric mean (CV%), n	300,000 (193.4), 78	210,000 (111.7), 8
$T_{½}$ (day)	Geometric mean (CV%), n	21.7 (196.8), 65	2.70 (154.4), 3
T_{last}	Median [min;max], n	170 [17.8; 617], 80	28.8 [13.9; 376], 11
[‡]A total of 5 patients had an early T_{max} (<1 days), the next lowest T_{max} occurs at 5.7 days. Early T_{max} may not be representative of the true maximal expansion, rather the amount of transgene present in the catheter from which sample was collected.			

Cellular kinetics in adult DLBCL patients

A summary of cellular kinetic parameters of tisagenlecleucel in DLBCL patients is provided in Table 8 below.

Table 8 Cellular kinetic parameters of tisagenlecleucel in r/r DLBCL patients by clinical response at month 3

Parameter	Summary statistics	Responding patients (CR and PR) N=35	Non-responding patients (SD/PD/Unknown) N=58
C_{max} (copies/μg)	Geometric mean (CV%), n	6210 (226.1), 35	5100 (372.6), 51
T_{max} (day)	Median [min;max], n	9.83 [5.78; 16.8], 35	8.86 [3.04; 27.7], 51
$AUC_{0\text{-}28d}$ (copies/μg*day)	Geometric mean (CV%), n	64300 (156.1), 33	64800 (301.1), 42
$T_{½}$ (day)	Geometric mean (CV%), n	91.3 (200.7), 22	15.4 (156.0), 34
T_{last}	Median [min;max], n	289 [18.0; 693], 35	57.0 [16.0; 374], 48

Distribution

In paediatric and young adult B-cell ALL patients, tisagenlecleucel has been shown to be present in the blood and bone marrow beyond 2 years (study B2101J). The blood to bone marrow partitioning of tisagenlecleucel in bone marrow was 47.2% of that present in blood at day 28 while at months 3 and 6 it distributes at 68.3% and 69%, respectively (Studies B2202 and B2205J). Tisagenlecleucel also traffics and persists in cerebrospinal fluid in paediatric and young adult B-cell ALL patients (Study B2101J) for up to 1 year.

In adult DLBCL patients (Study C2201), tisagenlecleucel has been detected for up to 2 years in peripheral blood and up to month 9 in bone marrow for complete responder patients. The blood to bone marrow partitioning in bone marrow was nearly 70% of that present in blood at day 28 and 50% at month 3 in both responder and non-responder patients.

Elimination

The elimination profile of Kymriah includes a bi-exponential decline in peripheral blood and bone marrow.

Linearity/non-linearity

There is no apparent relationship between dose and $AUC_{0\text{-}28d}$ or C_{max}.

Special populations

Elderly
The scatter plots of cellular kinetic parameters versus age (22-76 years) revealed no relevant relationship between cellular kinetic parameters ($AUC_{0\text{-}28d}$ and C_{max}) with age.

Gender
Gender is not a significant characteristic influencing tisagenlecleucel expansion in B-cell ALL and DLBCL patients. In Study B2202, 43% female and 57% male patients and in Study C2201 39% female and 61% male patients received Kymriah.

Race/ethnicity
There is limited evidence that race/ethnicity impact the expansion of Kymriah in paediatric and young adult ALL and DLBCL patients. In Studies B2202 and B2205J there were 79.8% Caucasian, 7.7% Asian and 12.5% other ethnic patients. In Study C2201 there were 88% Caucasian, 5% Asian, 4% Black or African American patients, and 3 patients (3%) of unknown race.

Body weight
In DLBCL patients, across the weight ranges (38.4 to 186.7 kg), the scatter plots of qPCR cellular kinetic parameters versus weight revealed no apparent relationship between cellular kinetic parameters with weight.

Prior transplantation
Prior transplantation did not impact the expansion/persistence of Kymriah in paediatric and young adult B-Cell ALL patients or DLBCL patients.

5.3 Preclinical safety data

Non-clinical safety assessment of Kymriah addressed the safety concerns of potential uncontrolled cell growth of transduced T cells *in vitro* and *in vivo* as well as dose-related toxicity, biodistribution and persistence. No such risks were identified based on these studies.

Carcinogenicity and mutagenicity

Genotoxicity assays and carcinogenicity studies in rodents are not appropriate to assess the risk of insertional mutagenesis for genetically-modified cell therapy products. No alternative adequate animal models are available.

In vitro expansion studies with CAR-positive T cells (Kymriah) from healthy donors and patients showed no evidence for transformation and/or immortalisation of T cells. *In vivo* studies in immunocompromised mice did not show signs of abnormal cell growth or signs of clonal cell expansion for up to 7 months, which represents the longest meaningful observation period for immunocompromised mouse models. A genomic insertion site analysis of the lentiviral vector was performed on Kymriah products from 14 individual donors (12 patients and 2 healthy volunteers). There was no evidence for preferential integration near genes of concern or preferential outgrowth of cells harbouring integration sites of concern.

Reproductive toxicity

No non-clinical reproductive safety studies were conducted as no adequate animal model is available.

Juvenile animal studies

Juvenile toxicity studies were not conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose
Sodium chloride
Human albumin solution
Dextran 40 for injection
Dimethylsulfoxide
Sodium gluconate
Sodium acetate
Potassium chloride
Magnesium chloride
Sodium-N-acetyltryptophanate
Sodium caprylate
Aluminium
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Should not be used after the date marked “EXP” on the pack.

The product should be administered immediately after thawing. After thawing, the product should be kept at room temperature (20°C-25°C) and infused within 30 minutes to maintain maximum product viability, including any interruption during the infusion.

6.4 Special precautions for storage

Store and transport below -120°C, e.g. in a container for cryogenic storage (Dewar) in the vapour phase of liquid nitrogen.

Store in the original protective envelope (Tyvek) containing the cassette protecting the infusion bag.

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 (EVA) infusion bag with polyvinyl chloride (PVC) tubing and a luer spike interconnector closed by a luer-lock cap containing either 10–30 mL (50 mL bags) or 30–50 mL (250 mL bags) cell dispersion.

Each infusion bag is placed into an aluminum cassette, then put in a plastic overwrap bag with absorbent sheets and sealed in a protective envelope (Tyvek).

One individual treatment dose comprises 1 to 3 infusion bags.

6.6 Special precautions for disposal and other handling

Inspection and thawing of the infusion bag(s)

Do not thaw the product until it is ready to be used.

The infusion bag should be placed inside a second, sterile bag during thawing to protect ports from contamination and avoid spills in the unlikely event of the bag leaking. Kymriah should be thawed at 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. The bag should be removed immediately from the thawing device and kept at room temperature (20°C-25°C) until infusion. If more than one infusion bag has been received for the treatment dose, the next bag should only be thawed after the contents of the preceding bag have been infused.

Kymriah should not be manipulated. For example, Kymriah should not be washed (spun down and resuspended in new media) prior to infusion.

The infusion bag(s) should be examined for any breaks or cracks prior to thawing. If the infusion bag appears to have been damaged or to be leaking, it should not be infused and should be disposed of according to local biosafety procedures (see section 4.2.).

Precautions to be taken for transport and disposal of the medicinal product

Kymriah should be transported within the facility in closed, break-proof, leak-proof containers.

Kymriah contains genetically-modified human blood cells. Local biosafety guidelines should be followed for unused medicinal product or waste material. All material that has been in contact with Kymriah (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local biosafety guidelines.

Revision date: 9 Dec 2019
Ref: EMA Sep 2018

Package leaflet: Information for the patient or carer

Kymriah 1.2 x 10^6 – 6 x 10^8 cells dispersion for infusion
tisagenlecleucel (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 (or your child) are given this medicine because it contains important information.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.
- 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.
- The information in this leaflet is for you or your child – but in the leaflet it will just say "you".

What is in this leaflet

1. What Kymriah is and what it is used for

What Kymriah is
Kymriah, also known as tisagenlecleucel, is made from some of your own white blood cells called T cells. T cells are important for your immune system (the body's defences) to work properly.

How does Kymriah work?
The T cells are taken from your blood and a new gene is put into the T cells so that they can then find the cells causing your cancer. When Kymriah is infused into your blood, the modified T cells will find the cancer cells and destroy them.

What Kymriah is used for
Kymriah is used to treat:
- **B-cell acute lymphoblastic leukaemia (B-cell ALL)** - a form of cancer that affects some other types of white blood cells. The medicine can be used in children and young adults up to 25 years of age with this cancer.
- **Diffuse large B-cell lymphoma (DLBCL)** - another form of cancer that affects some types of white blood cells, mostly in the lymph nodes. The medicine can be used in adults (18 years of age or older) with this cancer.

If you have any questions about how Kymriah works or why this medicine has been prescribed for you, ask your doctor.

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

You should not be given Kymriah:
- 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.

Warnings and precautions
Kymriah is made from your own white blood cells and should only be given to you.

Before you are given Kymriah you should tell your doctor if:
- You have had a stem cell transplant in the last 4 months. Your doctor will check if you have signs or symptoms of graft-versus-host disease. This happens when transplanted cells attack your body, causing symptoms such as rash, nausea, vomiting, diarrhoea and bloody stools.
- You have any lung, heart or blood pressure (low or raised) problems.
- You notice the symptoms of your cancer are getting worse. If you have leukaemia this might include fever, feeling weak, bleeding gums, bruising. If you have lymphoma, this might include unexplained fever, feeling weak, night sweats, sudden weight loss.
- You have an infection. The infection will be treated before the Kymriah infusion.
- You have had hepatitis B, hepatitis C or human immunodeficiency virus (HIV) infection.
- You are pregnant, think you may be pregnant, or plan to become pregnant (see sections "Pregnancy and breast-feeding" and "Contraception for women and men" below).
- You had a vaccination in the previous 6 weeks or are planning to have one in the next few months.

If any of the above apply to you (or you are not sure), talk to your doctor before being given Kymriah.

Test and checks
Before you are given Kymriah your doctor will:
- Check your lungs, heart and blood pressure.
- Look for signs of infection; any infection will be treated before you are given Kymriah.
- Check if your cancer is getting worse.
- Look for signs of graft-versus-host disease that can happen after a transplant.
- 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.

Talk to your doctor or nurse before you are given Kymriah if you have a history of:
- Fever, which may be a symptom of an infection. Your doctor will regularly check your blood counts as the number of blood cells and other blood components may decrease.
- Take your temperature twice a day for 3-4 weeks after treatment with Kymriah. If your temperature is high, see your doctor immediately.
- 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.
- Do not donate blood, organs, tissues or cells for transplants.
- There may be an effect on the results of some types of HIV test – ask your doctor about this.

Children and adolescents
- No formal studies have been performed in paediatric patients below 3 years of age in B-cell ALL. Kymriah should not be used in children and adolescents below 18 years of age to treat DLBCL. This is because Kymriah has not been studied in this age group.

Other medicines and Kymriah
Tell your doctor if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription. This is because other medicines can affect the way Kymriah works.

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

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

Before you are given Kymriah 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 Kymriah.

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 Kymriah in pregnant or breast-feeding women are not known, and it may harm your unborn baby or your newborn/infant.
- If you become pregnant or think you may be pregnant after treatment with Kymriah, talk your doctor immediately.
- You will be given a pregnancy test before treatment starts. Kymriah should only be given if the result shows you are not pregnant.

Contraception for women and men
Discuss pregnancy with your doctor if you have received Kymriah.

Driving and using machines
Do not drive, use machines, or take part in activities that need you to be alert for. Kymriah can cause problems such as altered or decreased consciousness, confusion and seizures (fits) in the 8 weeks following infusion.

Kymriah contains sodium, dimethylsulfoxide (DMSO) and dextran 40.
This medicine contains 24.3 to 121.5 mg sodium per dose. This is equivalent to 1 to 6% of the recommended maximum daily dietary intake of 2 g sodium for an adult. If you have not been previously exposed to dextran or DMSO you should be observed closely during the first minutes of the infusion period.

3. How Kymriah is given

Kymriah will always be given to you by a doctor.

Kymriah contains human blood cells. Your doctor handling Kymriah will therefore take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases.

Giving blood to make Kymriah
Kymriah is made from your own white blood cells.
- Your doctor will take some of your blood using a catheter placed in your vein (a procedure called 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 frozen and sent away to make Kymriah. It usually takes about 3 to 4 weeks to make Kymriah but the time may vary.
- Before you are given Kymriah, your doctor may give you a type of treatment called lymphodepleting chemotherapy for a few days to prepare your body.

Medicines given before Kymriah treatment
During the 30 to 60 minutes before you are given Kymriah 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 Kymriah
- Your doctor will check that the individual patient identifiers on the Kymriah infusion bag match up to you.
- Your doctor will give you Kymriah by infusion, which means it will be given as a drip through a tube in your vein. This usually takes less than 1 hour.
- Kymriah is a one-time treatment. It will not be given to you again.

After you are given Kymriah
- Plan to stay within 2 hours' travel from the hospital where you were treated for at least 4 weeks after you have been given Kymriah. Your doctor will recommend that you return to the hospital daily for at least 10 days and will consider whether you need to stay at the hospital as an in-patient for the first 10 days after infusion. This is so your doctor can check if your treatment is working and help you if you have any side effects.

If you miss an appointment, call your doctor or the hospital as soon as possible to reschedule.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately if you get any of the following side effects after the Kymriah infusion. They usually happen in the first 8 weeks after the infusion, but can also develop later:

Very common: may affect more than 1 in 10 people
- high fever and chills. These may be symptoms of a serious condition called cytokine release syndrome. Other symptoms of cytokine release syndrome are difficulty breathing, nausea, vomiting, diarrhoea, muscle pain, joint pain, low blood pressure, or dizziness/light-headedness. These symptoms almost always occur within the first 10 days after infusion.
- problems such as altered or decreased consciousness, delirium, confusion, agitation, seizures, difficulty speaking and understanding speech, loss of balance.
- feeling warm, fever, chills or shivering, sore throat or mouth ulcers may be signs of an infection.

Common: may affect up to 1 in every 10 people

- Rapid breakdown of tumour cells causing release of their contents into the bloodstream. This can interfere with the workings of various body organs, especially the kidneys, heart and nervous system (tumour lysis syndrome).

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*

- Pale skin, weakness, breathlessness
- Excessive or prolonged bleeding or bruising
- Reduced levels of one or more blood cell types
- Loss of appetite, weight loss
- Abnormal blood test results (high level of: uric acid, glucose; low level of: phosphorus, calcium, potassium, magnesium)
- Changes in blood test results that report on how the liver and kidneys are working (high levels of: liver enzymes, bilirubin, creatinine)
- Thirst
- Anxiety, irritability
- Confusion
- Headache
- Dizziness
- Fast heart beat
- Low or raised blood pressure
- Shortness of breath, laboured breathing, rapid breathing, fluid in the lungs
- Blue lips, hands and feet
- Cough
- Nausea, vomiting
- Abdominal pain, constipation, diarrhoea
- Skin rash
- Muscle and joint aches, muscle spasms, back pain
- Low urine output, dark urine
- Tiredness
- Difficulty sleeping
- Swollen ankles, limbs and face

Common: *may affect up to 1 in every 10 people*

- Signs and symptoms of blood clots
- Red or purple spots under the skin
- Very severe inflammation around the body (due to syndrome of immune activation)
- Stroke causing, for example, weakness, loss of balance, difficulty with speech, visual disturbance, difficulty swallowing
- Abnormal blood test results (high level of: phosphorus, magnesium, an enzyme called alkaline phosphatase to help detect liver disease, fibrin d-dimer, serum ferritin; low level of: sodium)
- Convulsion, fits (seizures)
- Involuntary tremor
- Tingling or numbness, also in fingers and toes
- Nerve pain
- Heart failure, stopped heart beat
- Irregular heart beat
- Hot flushes
- Nosebleeds
- Bloating (abdominal distension), accumulation of fluid in the abdomen

- Dry mouth, sore mouth, bleeding in the mouth, inflammation in the gums
- Jaundice
- Itching
- Excessive sweating, night sweats
- Flu-like illness
- Failure of multiple organs
- Leakage of fluids from blood vessels into surrounding tissue. This can lead to weight gain and difficulty breathing

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects to Novartis at https://psi.novartis.com or by sending email to safety.hk@novartis.com.
By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Kymriah

The following information is intended for doctors only.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the infusion bag label after EXP. The expiry date refers to the last day of that month.

Store and transport below -120°C. Do not thaw the product until it is ready to be used.

Do not use this medicine if the infusion bag is damaged or leaking.

This medicine contains genetically-modified blood cells. Local biosafety guidelines should be followed for unused medicine or waste material.

6. Contents of the pack and other information What Kymriah contains

- The active substance of Kymriah is called tisagenlecleucel. Each infusion bag of Kmyriah contains tisagenlecleucel cell dispersion at a batch-dependent concentration of autologous T cells genetically modified to express an anti-CD19 chimeric antigen receptor (CAR-positive viable T cells). 1-3 bags contain a total of $1.2 \times 10^6 – 6 \times 10^8$ CAR+ viable T cells.
- The other ingredients are glucose, sodium chloride, human albumin solution, dextran 40 for injection, dimethylsulfoxide, sodium gluconate, sodium acetate, potassium chloride, magnesium chloride, sodium-N-acetyltryptophanate, sodium caprylate, aluminium, and water for injections. See section 2, “Kymriah contains sodium, dimethylsulfoxide (DMSO) and dextran 40”.

What Kymriah looks like and contents of the pack
Kymriah is a cell dispersion for infusion. It is supplied as an infusion bag containing a cloudy to clear, colourless to slightly yellow dispersion of cells. Each bag contains 10 mL to 50 mL of dispersion.

The following information is intended for healthcare professionals only:

Preparation of the infusion bag

The timing of thaw of Kymriah and of infusion should be coordinated. Confirm the infusion time in advance, and adjust the start time for thaw so that Kymriah is available for infusion when the recipient is ready. Once Kymriah has been thawed and is at room temperature (20°C-25°C), it should be infused within 30 minutes to maintain maximum product viability, including any interruption during the infusion.

The infusion bag should be placed inside a second, sterile bag during thawing to protect ports from contamination and avoid spills in the unlikely event of the bag leaking. Kymriah should be thawed at 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. The bag should be removed immediately from the thawing device and kept at room temperature
(20°C-25°C) until infusion. If more than one infusion bag has been received for the treatment dose, the next bag should only be thawed after the contents of the preceding bag have been infused.

Kymriah should not be manipulated. For example, Kymriah should not be washed (spun down and resuspended in new media) prior to infusion.

The infusion bag(s) should be examined for any breaks or cracks prior to thawing. If the infusion bag appears to have been damaged or to be leaking, it should not be infused and should be disposed of according to local biosafety procedures.

Administration

Kymriah intravenous infusion should be administered by a healthcare professional experienced with immunosuppressed patients and prepared to manage anaphylaxis. Ensure that a minimum of four doses of tocilizumab and emergency equipment are available prior to infusion and during the recovery period.

The patient's identity should be matched with the patient identifiers on the infusion bag. Kymriah is for autologous use only. Kymriah should be administered as an intravenous infusion using latex-free intravenous tubing without a leukocyte depleting filter, at approximately 10 to 20 mL per minute by gravity flow. All contents of the infusion bags should be infused. Sterile sodium chloride 9 mg/mL (0.9%) solution for injection should be used to prime the tubing prior to infusion as well as rinse it afterwards. When the full volume of Kymriah has been infused, the infusion bag should 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 before handling or administering Kymriah

Kymriah contains genetically-modified human blood cells. Local biosafety guidelines should be followed for disposal.

All material that has been in contact with Kymriah (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local biosafety guidelines.

Kymriah should be transported within the facility in closed, break-proof, leak-proof containers.

Kymriah is prepared from autologous blood of the patient collected by leukapheresis. Patient leukapheresis material and Kymriah may carry a risk of transmitting infectious viruses to healthcare professionals handling the product. Accordingly, healthcare professionals should employ appropriate precautions (wearing gloves and glasses) when handling leukapheresis material or Kymriah to avoid potential transmission of infectious diseases.

Revision date: 9 Dec 2019
Ref: EMA Sep 2018