Kymriah® 1.2 x 10^6 – 6 x 10^8 cells dispersion for IV infusion (tisagenlecleucel)

Kymriah healthcare professional training material

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Kymriah product and therapeutic indications

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)

Kymriah is indicated for the treatment of:

- Paediatric and young adult patients up to and including 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

ALL, acute lymphoblastic leukaemia; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma.

Materials provided to healthcare professionals and patients

The following materials are provided in the Healthcare Professional information pack:

- Summary of Product Characteristics (SmPC)
- Educational material: Pharmacy/Cell Lab/Infusion Center Training Material
- Educational material: Healthcare Professional Training Material

The following materials are provided in the Patient information pack:

- SmPC Package leaflet
- Patient Alert Card
  - The patient should carry the Patient Alert Card at all times and show it to any healthcare provider
- Educational material: Patient Educational Leaflet
  - Includes instructions for the patient and information for their healthcare professional

SmPC, summary of product characteristics.

Kymriah Risk Management Plan (RMP): Key messages of additional risk minimisation measures

Controlled Distribution Program Objectives:

- To mitigate the safety risks associated with Kymriah treatment by ensuring that hospitals and their associated centres that dispense Kymriah infusion are specially qualified by Novartis
- Kymriah will only be supplied to hospitals and associated centres that are qualified and only if the healthcare professionals involved in the treatment of a patient have completed the educational program, and have on-site, immediate access to tocilizumab; in the exceptional case where tocilizumab is not available due to a shortage, the treatment centre must have access to suitable alternative measures instead of tocilizumab to treat cytokine release syndrome (CRS)

RMP, risk management plan; CRS, cytokine release syndrome.

Kymriah Risk Management Plan (RMP): Key messages of additional risk minimisation measures (continued)

Educational Program Objectives:

- **Pharmacy/Cell Lab/Infusion Centre Training Material:**
  - Inform about reception, storage, handling, thawing and preparation for infusion of Kymriah to mitigate a decrease in cell viability of Kymriah due to inappropriate handling of the product and subsequent potential impact on the efficacy/safety profile
- **Healthcare Professional Training Material:**
  - Mitigate the risk of severe or life-threatening CRS and neurological events by ensuring those, who prescribe, dispense, or administer Kymriah, are aware of how to manage the risks of CRS and neurological events
  - Inform about AE reporting in the respective registry for cellular therapy, while encouraging to spontaneously report the same AE(s), if causality to Kymriah is suspected, to Novartis or local Health Authorities
  - Counsel patients/guardians regarding:
    - Instances where Kymriah cannot be successfully manufactured and infusion cannot be provided, or the final manufactured product is Out-of-Specification (OOS)
    - The potential need for bridging chemotherapy and risk of progressive disease during manufacturing time, in addition to the risks of CRS and neurological events and actions to be taken

AE, adverse event; CRS, cytokine release syndrome.

Kymriah Risk Management Plan (RMP): Key messages of additional risk minimisation measures (continued)

Educational Program Objectives continued:

- **Patient Educational Leaflet**
  - Create awareness that there are instances where Kymriah cannot be successfully manufactured and infused, or final product is Out-of-Specification (OOS)
  - Inform about the potential need for bridging chemotherapy, associated adverse drug reactions, and the risk of progressive disease during the Kymriah manufacturing time
  - Educate patients/guardians on the risks of CRS and neurotoxicity, and when to seek medical attention
  - Inform about monitoring requirements and potential for hospitalisation following Kymriah infusion

CRS, cytokine release syndrome.

Reasons to Delay Kymriah Treatment

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Delay Kymriah infusion if the patient has:

Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions or hypotension) from preceding chemotherapies

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Active uncontrolled infection

Active graft-versus-host disease (GVHD)

Significant clinical worsening of leukaemia burden or rapid progression of lymphoma following lymphodepleting chemotherapy

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Kymriah-associated cytokine release syndrome (CRS)

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Cytokine release syndrome (CRS)

- CRS is a systemic inflammatory response associated with Kymriah cell expansion, activation and tumour cell killing
- CRS, including fatal or life-threatening events, has been frequently observed after Kymriah infusion
  - In paediatric and young adult patients with r/r B-cell ALL (ELIANA study, n=79): 77% of patients developed CRS of any grade (Penn grading system) and 48% developed grade 3 or 4 CRS
  - In adult patients with r/r DLBCL (JULIET study, n=115): 57% of patients developed CRS of any grade (Penn grading system) and 23% developed grade 3 or 4 CRS
- In almost all cases, development of CRS after Kymriah occurred between 1 to 10 days (median onset 3 days) in B-cell ALL patients and between 1 and 9 days (median onset 3 days) in adult DLBCL patients
- The median time to resolution of CRS was 8 days in B-cell ALL and 7 days in DLBCL patients
- Patients with CRS may require admission to the intensive care unit for supportive care

CRS, cytokine release syndrome.

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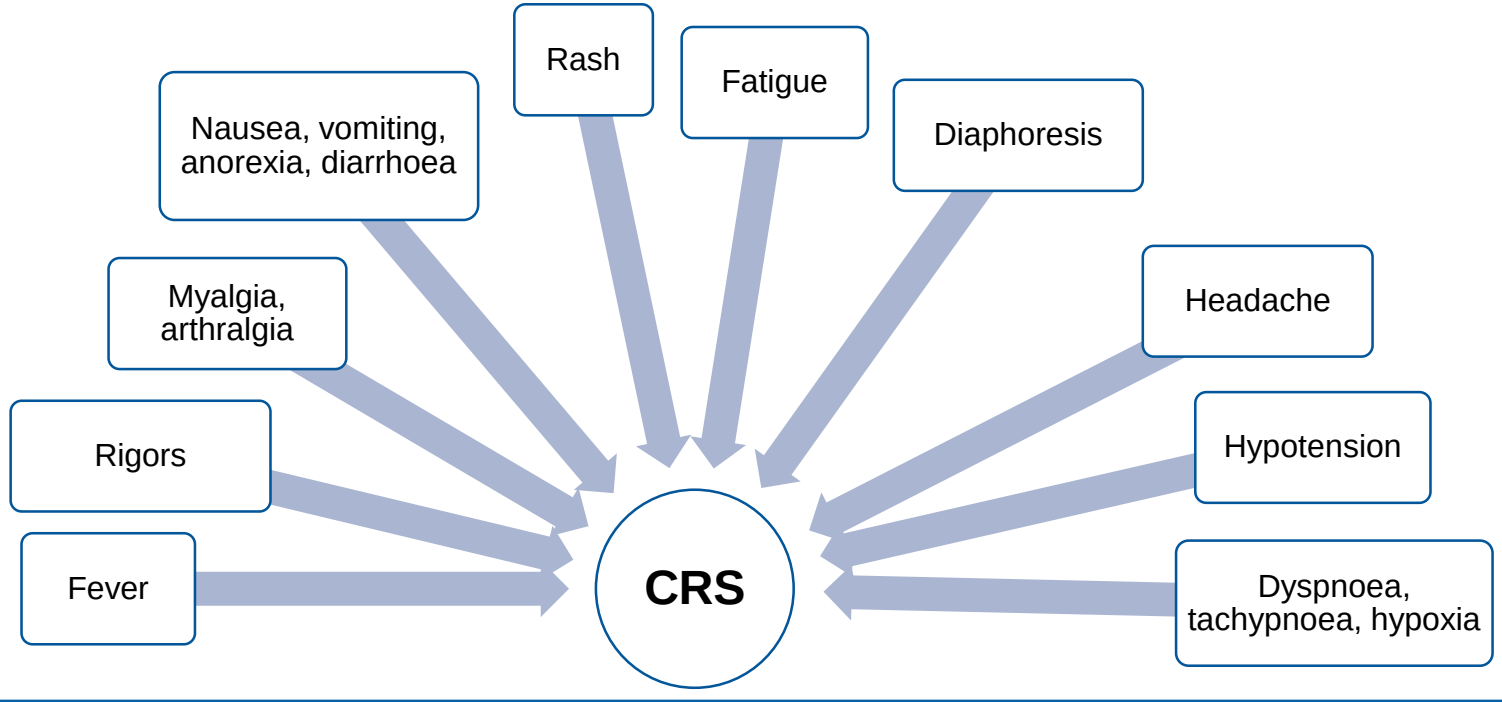
CRS signs and symptoms: patient presentation



Diagnosis based on clinical signs and symptoms[1-3]

References: 1. Lee DW et al. *Biol Blood Marrow Transplant.* 2019;25(4):625-638. **2.** Smith LT, Venella K. *Clin J Oncol Nurs.* 2017;21(2):29-34. **3.** Kymriah [summary of product characteristics]. Nuremberg, Germany: Novartis Pharma GmbH; 2020.

CRS-induced organ toxicity and associated adverse reactions

Hepatic	• Hepatic failure: elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), and hyperbilirubinaemia
Renal	• Acute kidney injury and renal failure, may require dialysis
Respiratory	• Respiratory failure, pulmonary oedema, may require intubation and mechanical ventilation
Cardiac	• Arrhythmia • Cardiac failure
Vascular	• Hypotension • Capillary leak syndrome
Haematological disorders including cytopenias >28 days following Kymriah infusion	• Leukopenia, neutropenia, thrombocytopenia, and/or anaemia • **Note:** Myeloid growth factors, particularly granulocyte macrophage-colony stimulating factor (GM-CSF), have the potential to worsen CRS symptoms and are not recommended during the first 3 weeks after Kymriah infusion or until CRS has resolved

CRS-induced organ toxicity and associated adverse reactions (continued)

Coagulopathy with hypofibrinogenaemia	• Disseminated intravascular coagulation (DIC) with low fibrinogen levels • May result in haemorrhage
Haemophagocytic lymphohistiocytosis / macrophage activation syndrome (HLH/MAS)	• **Note:** Severe CRS and HLH/MAS may have overlapping pathologies, clinical manifestations, and laboratory profiles • **Note:** When HLH or MAS occurs as a result of Kymriah, treat per CRS management algorithm. For late-onset, tocilizumab-refractory HLH/MAS, consider other anti-cytokine and anti-T cell therapies following institutional policy and published guidelines

Risk factors for severe CRS that could be established in ALL and DLBCL

Patients up to and including 25 years of age with r/r B-cell ALL	
Pre-infusion tumour burden	• High pre-infusion tumour burden, uncontrolled or accelerating tumour burden following lymphodepleting chemotherapy
Infection	• Active infection may increase the risk of severe CRS • Infections may also occur during CRS and may increase the risk of fatal events • Prior to administration of Kymriah, provide appropriate prophylactic and therapeutic treatment for infections, and ensure complete resolution of any existing infection
Onset of fever	• Early onset of fever can be associated with severe CRS
Onset of CRS	• Early onset of CRS can be associated with severe CRS
Adult patients with r/r DLBCL	
Pre-infusion tumour burden	• High tumour burden

Monitoring of CRS

- Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurological events and other toxicities
- Physicians should consider hospitalisation for the first 10 days post-infusion or at the first signs/symptoms of CRS and/or 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 (i.e., within 2 hours' travel) of a qualified clinical facility for at least 4 weeks following infusion

Management of CRS

- CRS should be managed based upon clinical presentation and according to the Kymriah CRS management algorithm as described in the SmPC and in the following slides
- 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
- Patients with medically significant cardiac dysfunction should be managed by standards of critical care and measures such as echocardiography should be considered

Management of CRS (continued)

- Anti-IL-6–based therapy such as tocilizumab* has been administered for moderate or severe CRS associated with Kymriah. One dose of tocilizumab per patient must be on site and available for administration prior to Kymriah infusion; the treatment centre must have access to additional doses of tocilizumab within 8 hours to manage CRS according to the CRS management algorithm per local prescribing information
  - In the exceptional case where tocilizumab is not available due to a shortage, the treatment centre must have access to suitable alternative measures instead of tocilizumab to treat CRS
- Due to the known lympholytic effect of corticosteroids*:
  - Do not use corticosteroids for premedication except in the case of a life-threatening emergency
  - Avoid the use of corticosteroids after infusion except in cases of life-threatening emergencies or in line with the CRS management algorithm
- Tumour necrosis factor (TNF) antagonists are not recommended for the management of Kymriah-associated CRS

*Kymriah continues to expand and persist despite administration of tocilizumab and corticosteroids.

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Kymriah CRS management algorithm

CRS Severity	Management
***Prodromal syndrome*:** **Low-grade fever, fatigue, anorexia**	Observe in person; exclude infection; administer antibiotics per local guidelines if neutropenic; provide symptomatic support
***CRS 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

Kymriah CRS management algorithm (continued)

CRS Severity	Management
***CRS 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 CRS • 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

Definition of high-dose vasopressors[1-4]

	Dose to be given for ≥ 3 hours	
Vasopressor	Weight-based dosing[a]	Flat dosing[b]
Norepinephrine monotherapy	≥ 0.2 mcg/kg/min	≥ 20 mcg/min
Dopamine monotherapy	≥ 10 mcg/kg/min	≥ 1000 mcg/min
Phenylephrine monotherapy	≥ 2 mcg/kg/min	≥ 200 mcg/min
Epinephrine monotherapy	≥ 0.1 mcg/kg/min	≥ 10 mcg/min
If on vasopressin	Vasopressin + norepinephrine equivalent (NE) of ≥ 0.1 mcg/kg/min[c]	Vasopressin + norepinephrine equivalent (NE) ≥ 10 mcg/min[d]
If on combination vasopressors (not vasopressin)	NE of ≥ 0.2 mcg/kg/min[c]	NE of ≥ 20 mcg/min[d]

[a] Weight-based dosing was extrapolated by dividing the flat dosing of a vasopressor by 100.

[b] If institutional practice is to use flat dosing.

[c] Vasopressin and Septic Shock Trial (VASST) norepinephrine equivalent equation: NE dose (weight-based dosing) = [norepinephrine (mcg/kg/min)] + [dopamine (mcg/kg/min) ÷ 2] + [epinephrine (mcg/kg/min)] + [phenylephrine (mcg/kg/min) ÷ 10][3]

[d] Vasopressin and Septic Shock Trial (VASST) norepinephrine equivalent equation: NE dose (flat dosing) = [norepinephrine (mcg/min)] + [dopamine (mcg/kg/min)] ÷ 2] + [epinephrine (mcg/min)] + [phenylephrine (mcg/min) ÷ 10][4]

References: 1. Lee DW et al. *Blood*. 2015;126(8):1048. **2.** Porter DL et al. *Sci Transl Med*. 2015;7(303):303ra139. https://stm.sciencemag.org/content/suppl/2015/08/31/7.303.303ra139.DC1. Accessed March 30, 2020. **3.** The University of Texas MD Anderson Cancer Center. Chimeric antigen receptor (CAR) cell therapy toxicity assessment and management – pediatric. https://www.mdanderson.org/documents/for-physicians/algorithms/clinical-management/clin-management-cytokine-release-pedi-web-algorithm.pdf. Published 2008. Accessed March 30, 2020. **4.** Russell JA et al. *N Engl J Med.* 2008;358(9):877-887. https://www.nejm.org/doi/suppl/10.1056/NEJMoa067373/suppl_file/nejm_russell_877sa1.pdf. Accessed March 30, 2020.

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Kymriah-associated neurological events

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Monitoring of neurological events

- Neurological events, in particular encephalopathy, confusional state or delirium, occur frequently with Kymriah and can be severe or life-threatening. Other manifestations include a depressed level of consciousness, seizures, aphasia and speech disorder
  - In paediatric and young adult patients with r/r B-cell ALL (ELIANA study, n=79): manifestations of encephalopathy and/or delirium of all grades occurred in 39% of patients, and grade 3 or 4 were seen in 10% of patients within 8 weeks after infusion
  - In adult patients with r/r DLBCL (JULIET study, n=115): manifestations of encephalopathy and/or delirium of all grades occurred in 20% of patients, and grade 3 or 4 were seen in 11% of patients

- The majority of neurological events occurred within 8 weeks following Kymriah infusion and were transient
  - Median time to onset: 8 days in B-cell ALL and 6 days in DLBCL
  - Median time to resolution: 7 days for B-cell ALL and 13 days for DLBCL

- Neurological events can be concurrent with CRS, following resolution of CRS, or in the absence of CRS

Monitoring for neurological events (continued)

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

Evaluation and management of neurological events

- Patients should be diagnostically worked up for neurologic events and managed depending on the underlying pathophysiology and in accordance with local standard of care
- Evaluation and grading of neurological events may include a neurologic assessment and evaluation of neurologic domains such as level of consciousness, motor symptoms, seizures, and signs of elevated intracranial pressure/cerebral oedema[1]
- If the neurological event is concurrent with CRS, please refer to the CRS management algorithm for treatment recommendations
- Consider anti-seizure medications (e.g. levetiracetam) for patients at high risk (prior history of seizure) or administer in the presence of seizure
- For encephalopathy, delirium or associated events: appropriate treatment and supportive care should be implemented as per local standard of care. In worsening events, consider a short course of steroids

Reference: 1. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638

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Physician to provide patient/guardian education

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Patient/Guardian education

Physicians need to hand out 3 materials: the Kymriah SmPC Package Leaflet, the Kymriah Patient Educational Leaflet and the Kymriah Patient Alert Card. Please review these materials with patients in detail

Patients/guardians should read and keep the SmPC Package Leaflet. Please review and explain the Leaflet with patients, guardians, and caregivers

Patients/guardians should read and keep Kymriah Patient Educational Leaflet to remind them of the signs and symptoms of CRS and neurological events, in addition to other clinically important side effects that require immediate medical attention

Patients/guardians should read the Kymriah Patient Alert Card in its entirety. Patient should carry the card with them at all times and show it to all healthcare providers

Patient/Guardian education (continued)

Counsel patients/guardians on the possibility that Kymriah may not be successfully manufactured and infusion cannot be provided if the final manufactured product is Out-of-Specification (OOS) and does not pass release tests. In some instances, a second manufacturing of Kymriah may be attempted. In case of OOS, the final product may be still provided as per physician's request, if supported by a positive benefit-risk assessment
Counsel patients/guardians on potential need for bridging therapy to stabilise the underlying disease while awaiting manufacturing and associated drug adverse reactions
Counsel patients/guardians on the risk of progressive disease during the Kymriah manufacturing time
Counsel patients/guardians that before getting Kymriah, a short course of lymphodepleting chemotherapy for conditioning may be given
Advise patients/guardians of the risk of CRS and neurological events and to contact their healthcare provider if experiencing signs and symptoms associated with CRS and neurological events

Patient/Guardian education (continued)

Patients/guardians should plan to stay within the proximity (i.e., within 2 hours' travel) of the qualified treatment centre for at least 4 weeks after receiving Kymriah treatment, unless otherwise indicated by the doctor
Instruct patients/guardians to return to the hospital daily for at least 10 days to allow monitoring for CRS, neurological events and other toxicities and potential need for hospitalization for side effects
Patients/guardians should be advised to measure the patient's temperature twice a day for 3-4 weeks after administration of Kymriah. If their temperature is elevated, they should see their doctor immediately
Due to the potential of Kymriah to cause problems such as altered or decreased consciousness, confusion, and seizures in the 8 weeks following infusion, patients should not drive, use machines, or take part in activities that require alertness
Patients/guardians should be advised that patient should not donate blood, organs, tissues or cells

Kymriah:
Adverse event reporting

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Adverse event reporting

- Healthcare providers should report AEs in the respective registry for cellular therapy and, in parallel, providers are encouraged to spontaneously report the same AEs, if causality to the Kymriah treatment is suspected
- Adverse reactions associated with Kymriah can be reported to Novartis , or to your local Health Authorities SFDA

Patient Safety Department Novartis Saudi Limited - Saudi Arabia
Toll Free Number: 8001240078
Phone: +966112658100
Fax: +966112658107
Email: adverse.events@novartis.com
Website: http://report.novartis.com/

Saudi Food and Drug Authority National Pharmacovigilance Center
Unified Contact Center: 19999
Fax: +966112057662
Email: npc.drug@sfda.gov.sa
Website: https://ade.sfda.gov.sa

- Importantly, when reporting adverse events, healthcare providers should always include the individual Kymriah Batch-identification number

KYMRIAH
Important note: Before prescribing, consult full prescribing information.
Presentation: Cell dispersion for infusion in one or more bags for intravenous use (tisagenlecleucel).
Indications: Kymriah is indicated for the treatment of:
Paediatric and young adult patients up to and including 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.
Dosage and administration:
Dose in paediatric and young adult B-cell ALL patients:
For patients 50 kg and below: 0.2 to 5.0 x 106 CAR-positive viable T-cells/kg body weight.
For patients above 50 kg: 0.1 to 2.5 x 108 CAR-positive viable T-cells (non-weight based).
Dose in adult DLBCL patients:
0.6 to 6.0 × 108 CAR-positive viable T-cells (non-weight based).
Manufacture and release of Kymriah usually takes about 3 to 4 weeks.
Kymriah must be administered in a treatment center that has been qualified by the Marketing Authorization Holder (MAH). Therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of hematological malignancies and trained for Kymriah administration and management of patients treated with Kymriah. A minimum of one doses of tocilizumab per patient for use in the event of cytokine release syndrome and emergency equipment must be available on site prior to infusion. Treatment centers should have timely access to additional doses of tocilizumab with in 8 hours.

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/m2 intravenous daily for 4 days) and cyclophosphamide (500 mg/m2 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/m2 intravenous daily for 2 days) and etoposide (150 mg/m2 intravenous daily for 3 days starting with the first dose of cytarabine).
DLBCL

The recommended lymphodepleting chemotherapy regimen is:
Fludarabine (25 mg/m2 intravenous daily for 3 days) and cyclophosphamide (250 mg/m2 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/m2 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 (Special warnings and precautions for use)

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 take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases as for any human-derived material.
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. 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. If the volume of Kymriah to be administered is ≤20 mL, intravenous push may be used as an alternative.
Clinical assessment prior to infusion:
Kymriah treatment should be delayed in some patient groups at risk (see warnings and precautions).

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 HIV, active HBV, or active HCV infection. Leukaphersis material from these patients will not be accepted for Kymriah manufacturing. Screening for HBV, HCV, and HIV must be performed in accordance with clinical guidelines before collection of cells for manufacturing.

Active central nervous system (CNS) leukemia or lymphoma:
There is limited experience of use of Kymriah in patients with active CNS leukemia and active CNS lymphoma. Therefore, the risk/benefit of Kymriah has not been established in these populations.
Safety monitoring prior to infusion:
Due to the risks associated with Kymriah, the infusion should be withheld if a patient has any of the following conditions:
Active uncontrolled serious adverse reactions from preceding chemotherapies especially pulmonary, cardiac and hypotension.
Active uncontrolled infection.
Active chronic graft versus host disease (GvHD).
Significant clinical worsening of leukemia burden or lymphoma following lymphodepleting chemotherapy.
Monitoring after infusion:
Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential cytokine release syndrome (CRS), neurological events and other toxicities.Physicians should consider hospitalization for the first 10 days post infusion or at the first signs/symptoms of CRS 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 (2 hours' travel) of a qualified clinical facility for at least 4 weeks following infusion.

Special populations
Pediatric population
B-cell ALL: No formal studies have been performed in pediatric 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.

Contraindications:
Hypersensitivity to tisagenlecleucel or to any excipient including dimethyl sulfoxide (DMSO) or dextran 40.
Contraindications of the lymphodepleting chemotherapy must be considered
Warnings and precautions:
Patient information: Patients should be educated to inform their treating physician immediately when signs of CRS or neurological events are observed. Patients should stay within 2 hours distance from Kymriah infusion location for 4 weeks.
Risk of CRS: Cytokine release syndrome, including fatal or life-threatening events, has been frequently observed after Kymriah infusion (see Undesirable effects) 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 8 days.See full prescribing information for CRS management.
Risk of neurological toxicities: Majority of severe or life-threatening events, in particular encephalopathy, confusional state or delirium, occurred within 8 weeks post infusion and were transient. The median time to onset of neurological events was 8 days and the median time to resolution was 7 days for B-cell ALL and 6 and 13 days for DLBCL, respectively.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.
Risk of infections: Delay start of therapy with Kymriah until active uncontrolled infections have resolved. As appropriate, administer prophylactic antibiotics and employ surveillance testing prior to and during treatment with Kymriah. Serious infections were observed in patients, some of which were life threatening or fatal. After Kymriah administration observe patient and ensure prompt management in case of signs of infection.
Risk of febrile neutropenia: Frequently observed after Kymriah infusion, may be concurrent with CRS. Appropriate management necessary.
Risk of low immunoglobulin levels: Preemptive measures such as infection precautions, antibiotic prophylaxis and immunoglobulin replacement should be taken according to age and standard guidelines.
Risk of prolonged cytopenias: Appropriate management necessary. Prolonged cytopenia associated with increased risk of infections. Myeloid growth factors particularly granulocyte macrophage-colony stimulating factor (GM-CSF), are not recommended until CRS resolved and typically not during the first 3 weeks after Kymriah infusion.
Risk of secondary malignancies: Patients treated with Kymriah may develop secondary malignancies or recurrence of their cancer and should be monitored life-long for secondary malignancies.
Risk of hypogammaglobulinaemia or agammaglobulinemia: Infection precautions, antibiotic prophylaxis and immunoglobulin replacement should be managed per age and standard guidelines.
Risks due to live vaccines: The safety of immunization with live viral vaccines during or following Kymriah treatment was not studied. Vaccination with live virus vaccines is not recommended at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Kymriah treatment, and until immune recovery following treatment with Kymriah.
Risk of tumor lysis syndrome (TLS): Patients with elevated uric acid or high tumor burden should receive allopurinol or alternative prophylaxis prior to Kymriah infusion. Continued monitoring for TLS following Kymriah administration should also be performed.

Prior stem cell transplantation: Kymriah infusion is not recommended within 4 months of undergoing an allogenic stem cell transplant (SCT) because of potential risk of worsening GVHD. Leukaphersis for Kymriah manufacturing should be performed at least 12 weeks after allogenic SCT.

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.

Fetal risk: There is no preclinical or clinical data to assess whether Kymriah constitutes a risk to a pregnant woman or the fetus.

Risk of viral reactivation: Not recommended in patients with hepatitis B because of potential risk of virus reactivation. Screening for HCV, HIV active HBV should be performed before collection of cells for manufacturing.

Risk of interference with serological testing: Due to limited and 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.

Risk due to content of dextran 40 and DMSO: contains 11 mg dextran 40 and 82.5 mg DMSO per mL known to possibly cause anaphylactic reactions following parenteral administration. Patients not previously exposed to dextran and DMSO should be observed closely during the first minutes of the infusion period.

Risk of driving and engaging in hazardous activities: in the 8 weeks following infusion these activities should be refrained due to risks for altered or decreased consciousness or coordination.

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 preclinical safety data). 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.
Adverse drug reactions:
Very common (≥10%): Anaemia, haemorrhage, febrile neutropenia, neutropenia, thrombocytopenia, arrhythmia, diarrhoea, nausea, vomiting, constipation, abdominal pain, pyrexia, fatigue, oedema, pain, chills, CRS, hypogammaglobulinaemia, infections (pathogen unspecified), viral-, bacterial- or fungal infections, neutrophil count decreased, platelet count decreased, aspartate aminotransferase increased, lymphocyte count decreased, white blood cell count decreased, haemoglobin decreased, decreased appetite, hypokalaemia, hypophosphataemia, hypomagnaesemia, hypocalcaemia, arthralgia, headache, encephalopathy, anxiety, delirium, sleep disorder, acute kidney injury, cough, dyspnoea, hypoxia, rash, hypotension, hypertension.
Common (≥1 to <10%): Haemophagocytic lymphohistiocytosis, leukopenia, pancytopenia, coagulopathy, lymphopenia, cardiac failure, cardiac arrest, visual impairment, stomatitis, abdominal distension, dry mouth, ascites, influenza like illness, asthenia, multiple organ dysfunction syndrome, hyperbiliburinaemia, infusion related reaction, GvHD, alanine aminotransferase increased, blood bilirubin increased, weight decreased, serum ferritin increased, blood fibrinogen decreased, international normalised ratio increased, fibrin D dimer increased, activated partial thromboplastin time prolonged, blood alkaline phosphatase increased, prothrombin time prolonged, hypoalbuminaemia, hyperglycaemia, hyponatraemia, hyperuricaemia, fluid overload, hypercalcaemia, TLS, hyperkalaemia, hyperphosphataemia, hypernatraemia, hypermagnesaemia, back pain, myalgia, musculoskeletal pain, dizziness, peripheral neuropathy, tremor, motor dysfunction, seizure, speech disorder, neuralgia, ataxia, oropharygeal pain, pulmonary oedema, nasal congestion, pleural effusion, tachypnoea, acute respiratory distress syndrome, pruritus, erythema, hyperhidrosis, night sweats, thrombosis, capillary leak syndrome.
Uncommon (≥0.1 to <1%): B-cell aplasia, ischemic cerebral infarction, lung infiltration, flushing.
Adverse reaction from spontaneous report (not known): anaphylactic reaction/infusion related reaction.
Interactions:
The co administration of agents known to inhibit T-cell function has not been formally studied. Administration of tocilizumab and steroids does not impact the expansion and persistence of CAR-T-cells as per the management of CRS treatment algorithm. The co administration of agents known to stimulate T-cell function has not been investigated and the effects are unknown.
Packs and prices: Country-specific.
Legal classification: Country-specific.
Version: V1.0
Tracking No. 2019-PSB/GLC-1066-s (initial Labeling)

Manufacturing failure and Out-of-Specification product

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Overview of the Out-of-Specification product release process

- In some cases, it may either not be possible to manufacture Kymriah or the release criteria may not be met due to patient-intrinsic factors or manufacturing failure
- In instances where the product cannot be manufactured or if the manufactured product is Out-of-Specification (OOS), the treating healthcare professional will be informed as early as possible by Novartis in accordance with Section 11.5 of Volume 4 of the GMP guideline specific to Advanced Therapy Medicinal Products (ATMPs), so the appropriate measures for the safety of the patient can be taken
- In the case a Kymriah batch proves to be OOS, Novartis will conduct an assessment of the anticipated efficacy and safety risks pertaining to this particular quality defect. The risk assessment will take into consideration prior clinical experience with Kymriah infusion in clinical trials and commercial setting as available and published literature. Importantly, the assessment does not provide infusion recommendations but is meant to inform the treating physician of the anticipated risks associated with a potential infusion of such a batch.
- The Novartis risk assessment will be communicated to the treating physician to allow the physician to perform an independent evaluation of risk-benefit of this batch and either request the product to be provided for infusion or consider any alternatives, such as other anti-cancer treatment or re-manufacturing of a new batch (if feasible taking into account the medical status of the patient)

ATMPs, advanced therapy medicinal products; OOS, out of specification.

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Thank you

This document has been approved by Saudi Food and Drug Authority (SFDA)
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