PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

**PrKYMRIAH®**

Tisagenlecleucel

# PART I: HEALTH PROFESSIONAL INFORMATION

Kymriah®, indicated for:

- adult patients with relapsed or refractory grade 1, 2, or 3a follicular lymphoma (FL) after two or more lines of systemic therapy.

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for Kymriah® please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html

Kymriah®, indicated for:

- pediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukemia (ALL) who are refractory, have relapsed after allogeneic stem cell transplant (SCT) or are otherwise ineligible for SCT, or have experienced second or later relapse.

- adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

has been issued market authorization without conditions.

## INDICATIONS

Kymriah® (tisagenlecleucel) is a CD19-directed genetically modified autologous T-cell immunocellular therapy indicated for the treatment of:

- pediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukemia (ALL) who are refractory, have relapsed after allogeneic stem cell

transplant (SCT) or are otherwise ineligible for SCT, or have experienced second or later relapse.

- adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.
- adult patients with relapsed or refractory grade 1, 2, or 3a follicular lymphoma (FL) after two or more lines of systemic therapy.

**Pediatrics**

*B-cell ALL*: No formal studies have been performed in relapsed or refractory B-cell ALL pediatric patients below 3 years of age.

*DLBCL and FL*: No formal studies in DLBCL and FL have included patients younger than 18 years of age.

**Geriatrics (≥65 years of age)**

*B-cell ALL*: The safety and efficacy of Kymriah in this population has not been established (see **10 ACTION AND CLINICAL PHARMACOLOGY**).

*DLBCL and FL*: No dose adjustment is required in patients 65 years of age or above (see **10 ACTION AND CLINICAL PHARMACOLOGY**).

**CONTRAINDICATIONS**

Kymriah is contraindicated in patients with known hypersensitivity to tisagenlecleucel or to any component of the product formulation, including dimethyl sulfoxide (DMSO) or dextran 40 (see **7 WARNINGS AND PRECAUTIONS**). For a complete listing, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

**SERIOUS WARNINGS AND PRECAUTIONS BOX**

**Serious Warnings and Precautions**

Cytokine release syndrome (CRS) is a common life-threatening adverse event, occurring in patients receiving Kymriah. Monitor for CRS after treatment with Kymriah. Provide supportive care as needed (see Description of selected adverse drug reactions and section Warnings and Precautions, Immune, Cytokine release syndrome).

Neurological toxicities, including immune effector cell-associated neurotoxicity syndrome (ICANS), which may be severe or life-threatening, can occur following treatment with Kymriah, including concurrently with CRS. Monitor for neurological events after treatment with Kymriah. Provide supportive care as needed (see **7 WARNINGS AND PRECAUTIONS**).

Kymriah should be administered by experienced healthcare professionals at specialized treatment centers (see **7 WARNINGS AND PRECAUTIONS**).

**DOSAGE AND ADMINISTRATION**

Kymriah must be administered in a treatment centre that has been qualified by Novartis Pharmaceuticals Canada Inc. Therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of haematological malignancies and trained for Kymriah administration and management of patients treated with Kymriah.

- Manufacture and release of Kymriah usually takes 3 – 4 weeks
- Leukapheresis material from patients who test positive for HIV, active HBV or active HCV infection will not be accepted for manufacturing of Kymriah. Screening for active HBV, active HCV and HIV must be performed in accordance with clinical guidelines *before* collection of cells for manufacturing.

**Dosing Considerations**

- For autologous use only – immediately prior to infusion, verify that the patient's identity matches the information on the patient specific infusion bag(s).

- For intravenous use only. Do NOT use a leukocyte depleting filter.
- Kymriah is intended for a single treatment.
- Ensure the availability of a minimum of 2 doses of tocilizumab per patient and emergency equipment prior to infusion. Treatment centers should ensure that additional doses of tocilizumab can be accessed within 8 hours of the previous dose**.**

**Active central nervous system (CNS) leukemia or lymphoma**

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

**Concomitant diseases**

Patients with active central nervous system (CNS) disorder or inadequate renal, hepatic, pulmonary or cardiac function were excluded from the studies. These patients are likely to be more vulnerable to the consequences of the adverse reactions described after Kymriah infusion and will require additional monitoring and management.

**Recommended Dose and Dosage Adjustment**

**Recommended Dose**

Kymriah is provided as a single-dose, one-time treatment, in a patient specific infusion bag(s).

***Pediatric and Young Adult B-cell ALL:***

- For patients 50 kg and below: 0.2 to 5.0 x $10^6$ chimeric antigen receptor (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).

***Adult Relapsed or Refractory Diffuse Large B-cell Lymphoma and Follicular Lymphoma:***

- 0.6 to 6.0 x $10^8$ CAR-positive viable T-cells (non-weight based).

**Pediatrics**

*B-cell ALL*: No formal studies have been performed in relapsed or refractory B-cell ALL pediatric patients below 3 years of age.

*DLBCL and FL*: No formal studies in diffuse large B-cell lymphoma and FL have been performed in pediatric patients younger than 18 years of age.

**Geriatrics (≥65 years of age)**

*B-cell ALL*: The safety and efficacy of Kymriah in this population has not been established (see **10**

**ACTION AND CLINICAL PHARMACOLOGY**).

*DLBCL and FL*: No dose adjustment is required in patients 65 years of age or above (see **10 ACTION AND CLINICAL PHARMACOLOGY**).

**Administration**

***Preparing the Patient for Kymriah Infusion***

***Pre-treatment conditioning (Lymphodepleting chemotherapy)***

- Confirm availability of Kymriah prior to initiating a lymphodepleting regimen.

For B-cell ALL and DLBCL indications, Kymriah is recommended to be infused 2 to 14 days after completion of the lymphodepleting chemotherapy. For FL, Kymriah is recommended to be infused 2 to 6 days after completion of the lymphodepleting chemotherapy.

Lymphodepleting chemotherapy may be omitted if a patient is experiencing significant cytopenia, e.g., white blood cell (WBC) count less than 1,000/microlitre within one week prior to infusion.

If there is a delay of more than 4 weeks between completing lymphodepleting chemotherapy and the Kymriah infusion and the WBC count is >1,000 cells/microlitre, then the patient should be re-treated with lymphodepleting chemotherapy prior to receiving Kymriah.

***Pediatric and Young Adult 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 hemorrhagic 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 x 3 days starting with the first dose of cytarabine).

***Adult Relapsed or Refractory Diffuse Large B-cell Lymphoma and Follicular Lymphoma:***

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 hemorrhagic cystitis with cyclophosphamide, or demonstrated a chemorefractory state to a cyclophosphamide-containing regimen administered

shortly before lymphodepleting chemotherapy, then the following regimen should be used in place of the fludarabine-cyclophosphamide regimen:

- Bendamustine (90 mg/m$^2$ intravenous daily for 2 days).

***Premedication:***

To minimize potential acute infusion reactions, it is recommended to premedicate patients with acetaminophen/paracetamol and diphenhydramine or another H1 antihistamine within approximately 30 to 60 minutes prior to Kymriah infusion. The prophylactic use of systemic corticosteroids should be avoided as it may interfere with the activity of Kymriah (see **7 WARNINGS AND PRECAUTIONS**).

***Clinical assessment prior to infusion***

Kymriah treatment should be delayed in certain patients with safety risk factors, including (see also: **7 WARNINGS AND PRECAUTIONS)**:

- 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 leukemia burden or rapid progression of lymphoma following lymphodepleting chemotherapy.

***Preparing Kymriah for infusion***

*Patient identity confirmation:* Prior to Kymriah infusion, the patient's identity must be matched with the patient identifiers on the Kymriah infusion bag(s).

*Inspection and thawing of the cryobag(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.

The infusion bag should be placed inside a second, bag, to avoid spills in case of a leak and to protect ports from contamination during thawing. The infusion bag(s) should be examined for any breaks or cracks prior to thawing. Kymriah should be thawed at 37°C using either water bath or dry thaw method until there is no visible ice in the infusion bag. The infusion bag should be removed immediately from the thawing device and should not be stored at 37°C after thawing is completed.

Inspect the contents of the thawed infusion bag for any visible cell clumps. If visible cell clumps remain, gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing.

Once Kymriah has been thawed and is at room temperature (20°C to 25°C), it should be infused within 30 minutes to maintain maximum product viability, including any interruption during the infusion.

If more than one bag has been received for the treatment dose, the additional bag(s) should not be thawed until after the contents of the first bag have been safely infused.

If the Kymriah bag appears to have been damaged or to be leaking or if clumps have not dispersed, it should not be infused, and should be disposed of according to local biosafety procedures. Novartis should then be contacted at 1-833-395-2278.

***Administration***

Kymriah should not be manipulated. For example, Kymriah should **not** be washed (spun down and resuspended in new media) prior to infusion. All contents of the infusion bag should be infused.

Kymriah should be administered as an intravenous infusion through latex free tubing. Do not use a leukocyte depleting filter. Infuse at approximately 10 to 20 mL per minute by gravity flow. Sodium chloride 9 mg/mL (0.9%) solution for injection should be used to prime the tubing prior to infusion and to rinse it afterwards. When the full volume of Kymriah has been infused, the Kymriah infusion bag should be rinsed with 10 to 30 mL sodium chloride 9 mg/mL (0.9%) solution for injection by back priming to assure as many cells as possible are infused into the patient.

In clinical trials intravenous push was an alternate method for the administration of low volumes of Kymriah. For special precautions for disposal see **11 STORAGE, STABILITY AND DISPOSAL**.

***Monitoring after infusion***

Following infusion with Kymriah patients should be monitored 2 to 3 times for at least the first week for signs and symptoms of cytokine release syndrome, neurological events and other toxicities. Physicians should consider hospitalization at the first signs and symptoms of cytokine release syndrome and/or neurological events.

Patients should be instructed to remain within proximity (2 hours of travel) of a qualified clinical facility for at least 4 weeks following infusion.

### Missed Dose

Not Applicable

## OVERDOSAGE

Not Applicable

## DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

### Dosage Forms, Strengths, Composition and Packaging

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|---|---|---|
| Intravenous infusion | Cell suspension for infusion in one or more bags.<br>$1.2 \times 10^6$ to $6.0 \times 10^8$ CAR-positive viable T cells, suspended in one or more patient-specific infusion bag(s).<br>The volume in the infusion bag ranges from 10 mL to 50 mL. | Dextran, dextrose, dimethylsulfoxide (DMSO), human serum albumin, plasma-Lyte A (multiple electrolytes for injection, Type 1, pH 7.4), and sodium chloride. |

### 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.

Appearance: colourless to slightly yellow suspension of cells.

## WARNINGS AND PRECAUTIONS

**Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.**

### General

Patients treated with Kymriah should not donate blood, organs, tissues, sperms, oocytes or other cells.

Treatment should only be administered in a treatment facility with personnel fully trained and approved for the care of patients receiving Kymriah infusion therapy. Fully trained staff will administer the Kymriah infusion using precautions for immunosuppressed patients. Emergency equipment must be available prior to infusion and during recovery period. See **4 DOSAGE AND ADMINISTRATION**.

Local guidelines should be followed for the supportive care of immunosuppressed and chemotherapy treated patients including infection management.

**Secondary Malignancies**

Patients treated with Kymriah may develop secondary malignancies or recurrence of their cancer. T-cell malignancies, including CAR-positive tumours, have occurred following treatment of hematologic malignancies with genetically modified autologous T-cell immunotherapies, including Kymriah treatment, which may present as soon as weeks following infusion, and may include fatal outcomes. Patients should be monitored life‑long for secondary malignancies, including those of T-cell origin. In the event that a secondary malignancy occurs, the company should be contacted to obtain instructions on patient samples to collect for testing (mykymriah.cart@novartis.com or 1-833-395-2278).

**Driving and Operating Machinery**

Due to the potential for neurological toxicity, patients receiving Kymriah are at risk for altered or decreased consciousness/coordination and/or seizures in the 8 weeks following infusion. Patients are advised to refrain from driving and/or engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery during this period.

**Endocrine and Metabolism**

***Tumour lysis syndrome***

Tumour lysis syndrome (TLS), which may be severe, has been observed among patients that received Kymriah. To minimize the risk of TLS, patients with elevated uric acid or high tumour burden should receive allopurinol, or an alternative prophylaxis, prior to Kymriah infusion. Signs, symptoms, and laboratory abnormalities of TLS including: hyperuricemia; hyperkalemia; hypocalcemia; hyperphosphatemia; acute renal failure; and elevated LDH; should be monitored and managed according to standard guidelines.

**Immune**

***Cytokine release syndrome***

Cytokine release syndrome (CRS), including life threatening or fatal events occurred frequently after Kymriah infusion. In almost all cases, development of CRS occurred between 1 to 10 days (median onset 3 days, range of 1-22 days) after Kymriah infusion in pediatric and young adult B-cell ALL patients, between 1 and 9 days (median onset 3 days, range of 1-51 days) after Kymriah infusion in adult DLBCL patients and between 1 to 14 days (median onset 4 days) after Kymriah infusion in adult FL patients. The median time to resolution of CRS was 8 days (range: 1-36 days) in B-cell ALL, 7 days in DLBCL patients (range: 2-30 days) and 4 days in FL patients (range: 1-24 days).

Signs and symptoms of CRS may include: high fever; rigors; myalgia; arthralgia; nausea; vomiting; diarrhea; diaphoresis; rash; anorexia; fatigue; headache; hypotension; dyspnea; tachypnea; tachycardia; and hypoxia. Organ dysfunction, including cardiac insufficiency, renal insufficiency and liver injury with accompanying elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT) or elevated total bilirubin may also be observed. In addition, disseminated intravascular coagulation (DIC) with low fibrinogen levels, capillary leak syndrome (CLS), macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH) may occur in the setting of CRS. Patients should be closely monitored for signs, symptoms, and laboratory abnormalities associated with these events including fever as outlined above. For onset of neurologic events, see **7 WARNINGS AND PRECAUTIONS – Neurologic**, below.

***Management of Cytokine Release Syndrome associated with Kymriah***

To reduce the risk or manage CRS complications (see above), patients treated with Kymriah may receive anti-interleukin-6 based intervention (e.g. tocilizumab) with or without a corticosteroid-based therapy. CRS management strategies may be implemented based on the most recent guidelines as appropriate (*eg*. institutional, provincial, international [*e.g*. ASCO], and academic).

A minimum of two doses of tocilizumab per patient must be available on site prior to Kymriah infusion. The treatment centers should ensure that additional doses of tocilizumab can be accessed within 8 hours of the previous dose. 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. Measures such as echocardiography should be considered. Tumour Necrosis Factor (TNF) antagonists are not recommended for management of Kymriah associated CRS.

Risk factors for severe CRS in pediatric and young adult B-cell ALL patients: are high tumour burden prior to Kymriah infusion; uncontrolled or accelerating tumour burden following

lymphodepleting chemotherapy, active infection and early onset of fever or CRS following Kymriah infusion. High tumour burden prior to Kymriah infusion was identified as a risk factor for developing severe CRS in adult DLBCL patients.

Prior to administration of Kymriah in pediatric and young adult B-cell ALL patients, efforts should be made to lower and control the patient's tumour burden.

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 CRS and may increase the risk of a fatal event. Coagulation parameters should be more frequently monitored in this setting in accordance with local standard of care, including management with cryoprecipitate or fibrinogen concentrate. In addition, clinically significant coagulopathy is often seen with moderate to severe CRS (Grade 3 and 4) and may continue as CRS is beginning to clinically resolve.

***Hypersensitivity Reactions***

Serious hypersensitivity reactions, including anaphylaxis, have been reported in the post-marketing setting following infusion of Kymriah (see section **8 Adverse Reactions**). All patients should be premedicated (see **4.3 Administration**) and closely monitored during the infusion period and institutional guidelines need to be followed for management of serious hypersensitivity reactions.

***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.

Patients enrolled in tisagenlecleucel studies are known to have a higher risk of infection at enrollment and to have a higher risk of intracurrent illness due to neutropenia, immunosuppression, lymphocyte-depleting chemotherapy, and the B cell aplasia from the direct action of the tisagenlecleucel cells infused. Prolonged neutropenia (laboratory grade 3 or 4 not resolved by Day 28) is a significant contributing factor to the risk of infections post-tisagenlecleucel infusion (see **8 ADVERSE REACTIONS**).

Serious infections, including life threatening or fatal infections, occurred in patients after Kymriah infusion. 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 CRS.

Febrile neutropenia was observed in patients after Kymriah infusion and may be concurrent with CRS. 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. In patients with low immunoglobulin levels pre-emptive measures such as immunoglobulin replacement and rapid 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 lymphodepleting chemotherapy and Kymriah and should be managed per 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 for pediatric ALL and DLBCL patients, and within 6 months for FL patients. 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 CRS symptoms and are not recommended during the first 3 weeks after Kymriah infusion and until CRS has resolved.

The degree and length of cytopenia may be additionally influenced by the history and the intensity of prior chemotherapies and radiation treatments, and prior history of chronic cytopenias and diminished bone marrow reserve.

***Hypogammaglobulinemia***

Hypogammaglobulinemia and agammaglobulinemia can occur in patients 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 immunization with live vaccines during or following Kymriah treatment has not been studied. Vaccination with live 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.

***Prior stem cell transplantation***

It is recommended that patients do not undergo allogenic stem cell transplant (SCT) within 4 months prior to receiving Kymriah because Kymriah may increase the risk of graft versus host disease (GVHD). Leukapheresis for Kymriah manufacturing should be performed at least 12 weeks after allogenic SCT.

***Viral reactivation***

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

***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 leukemia after prior anti-CD19 therapy.

***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 (see **9.3 Drug-Laboratory Test Interactions**).

**Neurologic**

Neurological toxicities (including immune effector cell-associated neurotoxicity syndrome (ICANS)), with signs and symptoms of encephalopathy, confusional state and/or delirium can occur with Kymriah and can be severe or life-threatening. Other manifestations include depressed level of consciousness, seizures, aphasia and speech disorder. The majority of neurological toxicities occurred within 8 weeks following Kymriah infusion and were transient. The median time to onset of the first neurological events occurring at any time following Kymriah infusion was 8 days in B-cell ALL, 6 days in DLBCL and 9 days for FL. The median time to resolution was 7 days for B-cell ALL, 13 days for DLBCL and 2 days for FL.

Neurological events can be concurrent with CRS, following resolution of CRS or in the absence of CRS (see **8 ADVERSE REACTIONS - Neurological/Neurotoxic events**).

Patients should be monitored for neurological events. To reduce the risk of or manage neurological toxicities (including ICANS) (see above), patients treated with Kymriah may receive supportive treatment based on the most recent guidelines as appropriate (*eg.* institutional, provincial, international or academic).

The possibility of opportunistic infections of the central nervous system should be considered in patients with neurological adverse events and appropriate diagnostic evaluations should be performed.

**Sexual Health**

***Reproduction***

Females of reproductive potential should use effective contraception (i.e., methods that result in less than 1% pregnancy rates) after Kymriah administration.

Sexually active males who have received Kymriah should use a condom during intercourse with a female of reproductive potential or a pregnant woman.

There are insufficient exposure data to provide a recommendation concerning the duration of contraception following treatment with Kymriah.

The intention to become pregnant or father a child after Kymriah therapy should be discussed with the treating physician. The potential risks to the pregnant woman and/or fetus should be explained.

***Fertility***

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

***Fetal risk***

There is a potential for Kymriah to cause fetal toxicity. It is not known if Kymriah constitutes a risk to a pregnant woman or the fetus, however Kymriah cells have the potential to be transferred to the fetus. This may cause fetal toxicity including B-cell lymphocytopenia. Therefore, Kymriah is not recommended for women who are pregnant, and pregnancy after Kymriah therapy should be discussed with the treating physician. Pregnant women and women of child-bearing potential should be advised of the potential risk to a fetus. See the prescribing information for lymphodepleting chemotherapy for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

**Special Populations**

**Pregnant Women**

Kymriah is not recommended for women who are pregnant. There are no available data with Kymriah use in pregnant women. No animal studies have been conducted with Kymriah to assess whether it can cause fetal harm when administered to a pregnant woman.

It is not known if Kymriah has the potential to be transferred to the fetus. Based on its mechanism of action, pregnant women who have received Kymriah may develop hypogammaglobulinemia and, if the transduced cells cross the placenta, they may cause fetal toxicity including B-cell lymphocytopenia. Similarly, newborns of mothers treated with Kymriah should also be assessed for hypogammaglobulinemia.

**Pregnancy testing**

The pregnancy status of females of reproductive potential should be verified prior to starting treatment with Kymriah.

**Breast-feeding**

It is unknown whether Kymriah cells are transferred into 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.

**Pediatrics (<18 years of age)**

*B-cell ALL*: No formal studies have been performed in relapsed or refractory B-cell ALL pediatric patients below 3 years of age.

*DLBCL and FL*: No formal studies in diffuse large B-cell lymphoma and FL have been performed in pediatric patients below 18 years of age.

**Geriatrics (≥ 65 years of age)**

*B-cell ALL*: The safety and efficacy of Kymriah in this population has not been established (see **10 ACTION AND CLINICAL PHARMACOLOGY**).

*DLBCL and FL*: No dose adjustment is required in patients 65 years of age or above (see **10 ACTION AND CLINICAL PHARMACOLOGY**).

## DRUG INTERACTIONS

### Overview

The co-administration of agents known to inhibit T-cell function has not been formally studied. T cells are known to be susceptible to immune suppressive agents. The benefit/risk of immuno-suppressive agents including but not limited to corticosteroids, cytotoxic chemotherapy,

immunophilins, mTOR inhibitors, should be considered as these agents can be lymphotoxic and may reduce the effectiveness of Kymriah. In patients who received tocilizumab and corticosteroids as per the cytokine release syndrome treatment algorithm, tisagenlecleucel transgene levels continued to expand and persist.

The co-administration of agents known to stimulate T-cell function has not been investigated and the effects are unknown.

**Drug-Drug Interactions**

**Pharmacokinetic interactions**

No pharmacokinetic drug interaction studies have been performed with Kymriah.

The immunization with live vaccines during or following Kymriah treatment has not been studied. Vaccination with live 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.

**Drug-Laboratory Test Interactions**

**Interference with HIV nucleic acid tests (NAT)**

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 may give a false positive result if the subject has received Kymriah.

**STORAGE, STABILITY AND DISPOSAL**

**Incompatibilities**

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

**Special precautions for storage**

Kymriah must be stored in a temperature monitored system at ≤ -120°C. The expiry date is indicated on the product label. Do not thaw the product until it is ready to be used.

**Special precautions for disposal**

Any unused product or waste material should be disposed of in accordance with local requirements.

Refer to local biosafety guidelines applicable for handling and disposal of products containing genetically-modified organisms.

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

Solid and liquid waste: All material having been in contact with Kymriah should be handled and disposed of as potentially infectious waste in accordance with local hospital procedures.

**SPECIAL HANDLING INSTRUCTIONS**

Kymriah contains genetically-modified blood cells. When handling Kymriah, healthcare professionals must take appropriate universal precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases as for any human-derived materials. Local biosafety guidelines applicable for handling and disposal of such products should be followed.

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**PATIENT MEDICATION INFORMATION**

**PrKYMRIAH®**

**[Kim-RAH-ya]**

**(Tisagenlecleucel)**

Read this carefully before you start taking Kymriah®. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Kymriah.

**Serious Warnings and Precautions**

The following serious side effects have been seen in people taking Kymriah:

- High fever, dizziness and light-headedness which may be symptoms of a serious condition called Cytokine Release Syndrome (CRS). Other symptoms of CRS are fast heartbeat, chills, difficulty breathing, nausea, vomiting, diarrhea, muscle pain, joint pain, or low blood pressure.
- Neurological problems like altered or decreased consciousness, delirium, confusion, agitation, seizures, difficulty speaking and understanding speech, loss of balance

Kymriah should only be administered by an experienced healthcare professional at specialized treatment centres.

**What Kymriah is**

Kymriah is made from some of your own normal white blood cells called T-cells. T-cells are important for your immune system (the body's defences) to work properly. Kymriah comes in infusion bags.

**What is Kymriah used for?**

Kymriah is used to treat:

- B-cell acute lymphoblastic leukemia (B-cell ALL) - a form of cancer composed of some types

of white blood cells that have become malignant. It can be used in children and young adults up to and including 25 years of age.

- Diffuse large B-cell lymphoma (DLBCL) - a form of cancer composed of some types of white blood cells that have become malignant, mostly in the lymph nodes. Kymriah can be used in adults (18 years of age or older) for whom DLBCL has returned after other treatments or when other treatments did not work.

For the following indication, Kymriah has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

- Kymriah is used to treat follicular Lymphoma (FL) - a form of cancer that affects types of white blood cells, called lymphocytes mostly in the lymph nodes. It is called 'follicular' lymphoma because the abnormal white blood cells usually develop in clumps called 'follicles' inside lymph nodes. Kymriah can be used in adults (18 years of age or older).

**What is a Notice of Compliance with Conditions (NOC/c)?**

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

**How does Kymriah work?**

The normal T-cells are taken from your blood and a new gene is put into the T-cells so that they can target the cancer cells more effectively. When Kymriah is infused into your blood, the modified T-cells find and kill the cancer cells.

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

**What are the ingredients in Kymriah?**

Medicinal ingredients: tisagenlecleucel

Non-medicinal ingredients: Dextran, dextrose, dimethylsulfoxide (DMSO), human serum albumin, plasma-Lyte A (multiple electrolytes for injection, Type 1, pH 7.4), and sodium chloride.

**Kymriah comes in the following dosage forms:**

Kymriah is provided as a cell suspension in one or more infusion bags. Kymriah is administered as an intravenous infusion for one time only.

**What Kymriah looks like:**

Kymriah is supplied as an infusion bag containing a cloudy to clear, colourless to slightly yellow suspension of cells (tisagenlecleucel).

**Do not use Kymriah:**

If you are allergic (hypersensitive) to tisagenlecleucel or any of the other ingredients of Kymriah.

If you think you may be allergic, ask your doctor for advice.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before receiving Kymriah. Talk about any health conditions or problems you may have, including:**

- If you have had a stem cell transplantation in the last 4 months. Your doctor will check if you have signs or symptoms of graft versus host disease (GvHD). This happens when transplanted cells attack your body, causing symptoms such as rash, nausea, vomiting, diarrhea and bloody stools.
- If you have any lung or heart or blood pressure problems.
- If you notice that the symptoms of your lymphoma or leukemia are getting worse. If you have leukemia this might include fever, feeling weak, bleeding gums, bruising. If you have lymphoma, this might included unexplained fever, feeling weak, night sweats, and/or sudden

weight loss.

- If you have had hepatitis B (HPV), hepatitis C (HBC) or human immunodeficiency virus (HIV) infection.
- If you had a vaccination in the previous 6 weeks or are planning to have one in the next few months.
- If you are pregnant, think you may be pregnant, or plan to become pregnant (see section Pregnancy and breast-feeding and Contraception for women and men).
- If you have an infection. The infection will be treated before the Kymriah infusion.

**Monitoring before and after your treatment with Kymriah**

**Before receiving Kymriah**

Before you are given Kymriah infusion, your doctor will:

- Check your lung, heart and blood pressure functions.
- Check to see if you are pregnant.
- Look for any signs of infection. Any active infection will be treated before administration of Kymriah.
- Check if your lymphoma or leukemia is getting worse.
- Check for signs of a medical complication called “graft versus host disease (GvHD)” that may occur usually after a prior transplant.
- Check your blood for uric acid and how many cancer cells there are in the blood. This will show if you are likely to have ‘tumour lysis syndrome (TLS)’ - if needed, you will be given medicines to help reduce the chance of this.
- Check if you have any antibodies to hepatitis B or C or HIV in the blood.

**After receiving Kymriah**

- Your doctor will regularly monitor your blood counts after you receive Kymriah as you may experience a reduction in the number of blood cells and blood components such as decreases in different types of normal white blood cells and/or a reduction on your normal antibodies that help fight infection.
- Your doctor will regularly check for signs of CRS or neurological problems
- Some types of HIV testing may be affected – ask your doctor about this.

- Do not donate blood, organs, tissues, sperms, oocytes and other cells.
- You should be monitored life-long to check if your lymphoma or leukemia returns or a new cancer, such as cancer of a type of white blood cells called T-cells, occurs. In the event that a new cancer occurs, your doctor or you should contact Novartis (mykymriah.cart@novartis.com or 1-833-395-2278).
- You should be monitored for neurological events.
- You should be monitored for signs and symptoms of infection.
- You should be monitored for signs and symptoms of TLS.
- You should be monitored for signs of serious allergic reactions or hypersensitivity reactions both during and after treatment with Kymriah. Signs include fever, chills, shivering, nausea, vomiting, tiredness, difficulty breathing and dizziness.

**Children**

Kymriah has not been studied in children and adolescents below 18 years of age with diffuse large B-cell lymphoma or follicular lymphoma and should not be administered in this age group for diffuse large B-cell or follicular lymphoma.

**Older people (65 years of age or above)**

Patients aged 65 years or above with diffuse large B-cell or follicular lymphoma can be administered Kymriah in the same way as younger adults.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with Kymriah:**

- 'Live' vaccines – in particular, do not receive 'live' vaccines:

  - In the 6 weeks before being given a short course of chemotherapy ("lymphodepleting" chemotherapy) to prepare your body for the Kymriah cells

  - During Kymriah treatment

  - After treatment while the immune system is recovering.

**Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you might be pregnant or are planning to have a baby, ask your doctor for advice before taking Kymriah. 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.

Your doctor will check with you if you are pregnant.

If you become pregnant or think you may be pregnant after treatment with Kymriah, talk to your doctor immediately.

Your doctor will discuss with you the potential risk(s) of receiving Kymriah during pregnancy or breast-feeding.

**Contraception for women and men**

Women of child-bearing potential should use effective birth control after being given Kymriah. Ask your doctor about options of effective birth control.

Sexually active males receiving Kymriah should use a condom for intercourse.

Discuss pregnancy or fathering a child 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. Kymriah can cause problems such as altered or decreased consciousness, confusion and seizures (fits) in the 8 weeks following infusion.

**How you will receive Kymriah:**

Kymriah will always be given to you by a qualified health care professional in a qualified treatment center.

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

**Collection of blood to manufacture Kymriah**

Kymriah is made from your own white blood cells.

- Your doctor will take some of your blood using a tube placed in your vein - this is called

'leukapheresis'. This can take 3 to 6 hours and may need to be repeated.

- Your blood cells are frozen and sent away to manufacture Kymriah. It takes about 3 to 4 weeks to make Kymriah, but the time may vary.
- While awaiting Kymriah manufacture, the underlying disease may worsen and progress and your healthcare provider may give you therapy to stabilize your cancer. This may induce side effects which can be severe or life-threatening. The treating physician will inform you about potential side effects of this therapy.
- In addition, before you get Kymriah, your healthcare provider may give you chemotherapy for a few days to prepare your body.
- Kymriah is a treatment that is manufactured specifically for you. There are situations where Kymriah cannot be successfully manufactured and be given to you. In some cases, a second manufacturing of Kymriah may be attempted.

**Medicines given before Kymriah administration**

During the 30 to 60 minutes before being given Kymriah you may receive other medicines to help to reduce infusion reactions and/or fever. These may include acetaminophen and an H1 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 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. During the infusion, your doctor will check if you have difficulty breathing or dizziness (possible symptoms of allergic reactions).

Kymriah is a one-time treatment.

**After you are given Kymriah**

Plan to stay within proximity (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 2 to 3 times a week for at least the first week and will consider whether you

need to stay at the hospital as an in-patient after infusion. This is so your doctor can check if your treatment is working and help you if you have any side effects.

**What are possible side effects from using Kymriah?**

Listed below are the most common (but not all) possible side effects you may feel when taking Kymriah. If you experience any side effects, including those not listed here, contact your healthcare professional.

**Very common:**

- Abdominal pain, constipation, weight loss
- Muscle weakness, muscle spasms
- Symptoms of high blood sugar like thirst, low urine output, dark urine, dry flushed skin, irritability
- Swelling of the arms or legs

**Common:**

- Swelling of the belly
- Changes or loss of vision
- Sore throat, stuffy nose, flu-like symptoms
- Bloating, mouth sores, dry mouth
- Skin reactions such as rash, hot flushes, night sweats, itching (pruritus), skin reddening (erythema), excessive sweating (hyperhidrosis)
- Muscle cramps
- Excessive emotional distress (anxiety)
- Sleep disturbances

| **Serious side effects and what to do about them** | | |
|---|---|---|
| Symptom / effect | Talk to your healthcare professional | |
| | Only if severe | In all cases |
| **VERY COMMON** | | |

| Serious side effects and what to do about them | | |
|---|---|---|
| Symptom / effect | Talk to your healthcare professional | |
| | Only if severe | In all cases |
| Feeling warm, fever, chills or shivering, coughing (possible symptoms of an infection) | | √ |
| Bleeding or bruising more easily (possible symptoms of low levels of cells in the blood known as platelets) | | √ |
| Frequent infections, weakness, fatigue, fever, chills and/or shivering, sore throat, mouth ulcers, rash, swelling, yellow or pale skin, yellow eyes, uncontrolled internal or external bleeding, blood in the urine, breathlessness, abnormal body movement, irritability (possible symptoms of blood disorders) | | √ |
| Extreme tiredness, weakness and shortness of breath (may be symptoms of a lack of red blood cells) | | √ |
| High fever, chills, muscle pain, joint pain, nausea, vomiting, diarrhea, excessive sweating, rash, loss of appetite, fatigue, headache, dizziness/light-headedness, shortness of breath, heavy breathing, rapid breathing, blue discolouration of lips or extremities (possible symptoms of CRS) | | √ |
| Side effects affecting the respiratory organs, like, coughing, rapid breathing, painful breathing, shortness of breath or labored breathing, breathlessness (possible symptom of pulmonary oedema, a build-up of fluid in the alveoli (air spaces) in the lungs, which keeps oxygen from getting into the blood) | | √ |
| Personality changes, headache, confusion, paralysis of part or all of the body, stiff neck, abnormal speech and eye movement (possible symptoms of encephalopathy or metabolic encephalopathy) | | √ |
| Dizziness, light-headedness (possible symptoms of hypotension) | | √ |
| Viral or bacterial or fungal infections | | √ |
| Swollen ankles (possible symptoms of low levels of albumin in the blood) | | √ |
| Blue discolouration of lips or extremities (hypoxia) | | √ |

| Serious side effects and what to do about them | | |
|---|---|---|
| Symptom / effect | Talk to your healthcare professional | |
| | Only if severe | In all cases |
| Severely decreased urine output (possible symptoms of acute kidney injury) | | √ |
| **COMMON** | | |
| Tiredness, confusion, muscle twitching, convulsions (possible symptoms of low level of sodium in blood) | | √ |
| Side effects affecting the nervous system, including involuntary shaking of the body (tremor), tingling or numbness (paresthesia), impaired memory or thinking (cognitive disorders), sensation of numbness or tingling in finger and toes (peripheral neuropathy), uncontrollable movements or actions of the body including tremors, jerks, twitches, spasms, contractions, or gait problems (motor dysfunction), difficulty in speaking or understanding speech (speech disorders) | | √ |
| Fever, malaise, yellow colour of your skin and eyes (possible symptoms of hemophagocytic lymphohistiocytosis) | | √ |
| Producing less urine than normal and/or muscle spasms (possible symptoms of tumour lysis syndrome) | | √ |
| Weakness or paralysis of limbs or face, difficulty speaking (possible symptoms of a stroke) | | √ |
| Convulsions, fits (seizures) | | √ |
| Severe nerve pain (neuralgia) | | √ |
| Fast and/or irregular heartbeat, breathlessness, difficulty breathing when lying down, swelling of the feet or legs, stopped heartbeat (possible symptoms of heart failure, worsening of heart failure or cardiac arrest) | | √ |
| Swelling and oedema (possible symptoms of capillary leak syndrome in context of CRS) | | √ |
| High fever, chills, difficulty to breath, yellow skin and eyes, bloody stools, severely decreased urine output (possible symptoms of multiple organ dysfunction syndrome) | | √ |
| Involuntary shaking of the body, difficulty writing, difficulty expressing thoughts verbally, impaired attention, | | √ |

| Serious side effects and what to do about them | | |
|---|---|---|
| Symptom / effect | Talk to your healthcare professional | |
| | Only if severe | In all cases |
| sleepiness (*possible symptoms of Immune Effector Cell-Associated Neurotoxicity Syndrome - ICANS*) | | |
| State of severe confusion *(delirium)* | | **√** |
| Fever, chills, shivering, nausea, vomiting, tiredness, dizziness, pain where the infusion needle is inserted, blisters, itching, and/or shortness of breath or wheezing during or shortly after infusion (possible infusion reaction) | | **√** |
| **UNCOMMON** | | |
| Difficulty of control of movements *(ataxia)* | | **√** |
| **UNKNOWN** | | |
| Difficulty breathing, dizziness (possible symptoms of allergic reactions) | | **√** |
| Weakness or numbness in the arms or legs, worsening of or loss of vision, having fixed and irrational thoughts that are not shared by others, headache, impaired memory or thinking, unusual behaviors (possible symptoms of neurotoxicity) | | **√** |
| Symptoms of new cancer including new lymphoma or leukemia from a type of white blood cells called T -cells. If you have T-cell leukemia this might include symptoms of fever, feeling weak, bleeding gums, bruising. If you have T-cell lymphoma, this might include symptoms of unexplained fever, feeling weak, night sweats, sudden weight loss. | | **√** |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

a. Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or

b. Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Reporting Suspected Side Effects**

**For the general public:** Should you experience a side effect following immunization, please report it to your doctor, nurse, or pharmacist.

Should you require information related to the management of the side effect, please contact your healthcare provider. The Public Health Agency of Canada, Health Canada and Novartis Pharmaceuticals Canada Inc. cannot provide medical advice.

**For healthcare professionals:** If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php) and send it to your local Health Unit.

**If you want more information about Kymriah:**

**1** Talk to your healthcare professional

**2** Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website http://hc-sc.gc.ca/index-eng.php; the manufacturer's website http://www.novartis.ca, or by calling 1-800-363-8883.

This leaflet was prepared by:

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