HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KYMRIAH safely and effectively. See full prescribing information for KYMRIAH.

KYMRIAH® (tisagenlecleucel) suspension for intravenous infusion

Initial U.S. Approval: 2017

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES

See full prescribing information for complete boxed warning.

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving KYMRIAH. Do not administer KYMRIAH to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids. (2.3, 2.4, 5.1)**
- **Neurological toxicities, 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. (5.2)**
- **KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS. (5.3)**

----------INDICATIONS AND USAGE----------

KYMRIAH is a CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of:

- Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. (1.1)
- Adult patients with relapsed or refractory (r/r) 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.

  Limitation of Use: KYMRIAH is not indicated for treatment of patients with primary central nervous system lymphoma (1.2)

----------DOSAGE AND ADMINISTRATION----------

For autologous use only. **For intravenous use only.**

- Administer a lymphodepleting regimen if needed before infusion of KYMRIAH (2.3)
- Do NOT use a leukodepleting filter.
- Verify the patient's identity prior to infusion. (2)
- Premedicate with acetaminophen and an H1-antihistamine. (2.3)
- Confirm availability of tocilizumab prior to infusion. (2.3, 5.1)
- Dosing of KYMRIAH is based on the number of chimeric antigen receptor (CAR)-positive viable T cells.
- **Pediatric and Young Adult B-cell ALL (up to 25 years of age)**
  - For patients 50 kg or less, administer 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg body weight intravenously. (2.1)
  - For patients above 50 kg, administer 0.1 to 2.5 x 10^8 total CAR-positive viable T cells (non-weight based) intravenously. (2.1)
- **Adult Relapsed or Refractory Diffuse Large B-cell Lymphoma**
  - Administer 0.6 to 6.0 x 10^8 CAR-positive viable T cells intravenously. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- **Pediatric and Young Adult B-cell ALL (up to 25 years of age)**

A single dose of KYMRIAH contains 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg of body weight for patients 50 kg or less, or 0.1 to 2.5 x 10^8 CAR-positive viable T cells for patients more than 50 kg, suspended in one to three patient-specific infusion bag(s) for i.v. infusion. (3)

- **Adult Relapsed or Refractory Diffuse Large B-cell Lymphoma**

A single dose of KYMRIAH contains 0.6 to 6.0 x 10^8 CAR-positive viable T cells suspended in one to three patient-specific infusion bag(s) for i.v. infusion. (3)

----------CONTRAINDICATIONS----------

None. (4)

---------- WARNINGS AND PRECAUTIONS----------

- Hypersensitivity Reactions: Monitor for hypersensitivity reactions during infusion. (5.4)
- Serious Infections: Monitor patients for signs and symptoms of infection; treat appropriately. (5.5)
- Prolonged Cytopenias: Patients may exhibit ≥ Grade 3 cytopenias for several weeks following KYMRIAH infusion. Prolonged neutropenia has been associated with increased risk of infection. (5.6)
- Hypogammaglobulinemia: Monitor and provide replacement therapy until resolution. Assess immunoglobulin levels in newborns of mothers treated with KYMRIAH. (5.7)
- Secondary Malignancies: In the event that a secondary malignancy occurs after treatment with KYMRIAH, contact Novartis Pharmaceuticals Corporation at 1-844-4KYMRIAH. (5.8)
- Effects on Ability to Drive and Use Machines: Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks after receiving KYMRIAH. (5.9)

----------ADVERSE REACTIONS----------

Pediatric and Young Adult B-cell ALL (up to 25 years of age): The most common adverse reactions (incidence greater than 20%) are cytokine release syndrome, hypogammaglobulinemia, infections-pathogen unspecified, pyrexia, decreased appetite, headache, encephalopathy, hypotension, bleeding episodes, tachycardia, nausea, diarrhea, vomiting, viral infectious disorders, hypoxia, fatigue, acute kidney injury, edema, cough and delirium. (6)

Adult Relapsed or Refractory Diffuse Large B-cell Lymphoma: The most common adverse reactions (incidence greater than 20%) are CRS, infections-pathogen unspecified, pyrexia, diarrhea, nausea, fatigue, hypotension, edema and headache. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2020

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FULL PRESCRIBING INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving KYMRIAH. Do not administer KYMRIAH to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids *[see Dosage and Administration (2.3, 2.4), Warnings and Precautions (5.1)].***
- **Neurological toxicities, 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 Warnings and Precautions (5.2)]*.**
- **KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS *[see Warnings and Precautions (5.3)]*.**

1 INDICATIONS AND USAGE

KYMRIAH is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of:

1.1 Pediatric and Young Adult Relapsed or Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL)

Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

1.2 Adult Relapsed or Refractory (r/r) Diffuse Large B-Cell Lymphoma (DLBCL)

Adult patients with relapsed or refractory (r/r) 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.

Limitation of Use: KYMRIAH is not indicated for treatment of patients with primary central nervous system lymphoma.

2 DOSAGE AND ADMINISTRATION

For autologous use only. For intravenous use only.

2.1 Dosage in Pediatric and Young Adult Relapsed or Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL)

KYMRIAH is provided as a single-dose for infusion containing a suspension of chimeric antigen receptor (CAR)-positive viable T cells.

Based on the patient weight reported at the time of leukapheresis:

- Patients 50 kg or less: administer 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg body weight
- Patients above 50 kg: administer 0.1 to 2.5 x 10^8 CAR-positive viable T cells

2.2 Dosage in Adult Relapsed or Refractory (r/r) Diffuse Large B-cell lymphoma (DLBCL)

KYMRIAH is provided as a single-dose for infusion containing a suspension of chimeric antigen receptor (CAR)-positive viable T cells.

- For adult patients: administer 0.6 to 6.0 x 10^8 CAR-positive viable T cells

2.3 Administration

Preparing Patient for KYMRIAH Administration with Lymphodepletion

- Confirm availability of KYMRIAH prior to starting the lymphodepleting regimen.

Pediatric and Young Adult Relapsed or Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL)

- Lymphodepleting chemotherapy: 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). Infuse KYMRIAH 2 to 14 days after completion of the lymphodepleting chemotherapy.

Adult Relapsed or Refractory (r/r) Diffuse Large B-cell lymphoma (DLBCL)

- Lymphodepleting chemotherapy: Fludarabine (25 mg/m^2 i.v. daily for 3 days) and cyclophosphamide (250 mg/m^2 IV daily for 3 days starting with the first dose of fludarabine).
- Alternate lymphodepleting chemotherapy: bendamustine 90 mg/m^2 i.v. daily for 2 days if a patient experienced a previous Grade 4 hemorrhagic cystitis with cyclophosphamide or demonstrates resistance to a previous cyclophosphamide containing regimen.
- Infuse KYMRIAH 2 to 11 days after completion of the lymphodepleting chemotherapy.
- Lymphodepleting chemotherapy may be omitted if a patient's white blood cell (WBC) count is less than or equal to 1 x 10^9/L within 1 week prior to KYMRIAH infusion.

Preparation of KYMRIAH for Infusion and Administration

Delay the infusion of KYMRIAH if a patient has unresolved serious adverse reactions (including pulmonary reactions, cardiac reactions, or hypotension) from preceding chemotherapies, active uncontrolled infection, active graft versus host disease (GVHD), or worsening of leukemia burden following lymphodepleting chemotherapy *[see Warnings and Precautions (5.1)]*.

A KYMRIAH dose may be contained in one to three cryopreserved patient-specific infusion bag(s). Verify the number of bags received for the dose of KYMRIAH with the Certificate of Conformance (CoC) and Certificate of Analysis (CoA). Coordinate the timing of thaw of KYMRIAH and infusion in the following manner. Confirm the infusion time in advance, and adjust the start time for thaw so that KYMRIAH is available for infusion when the recipient is ready. If more than one bag has been received for the treatment dose, thaw 1 bag at a time. Wait to thaw/infuse the next bag until it is determined that the previous bag is safely administered.

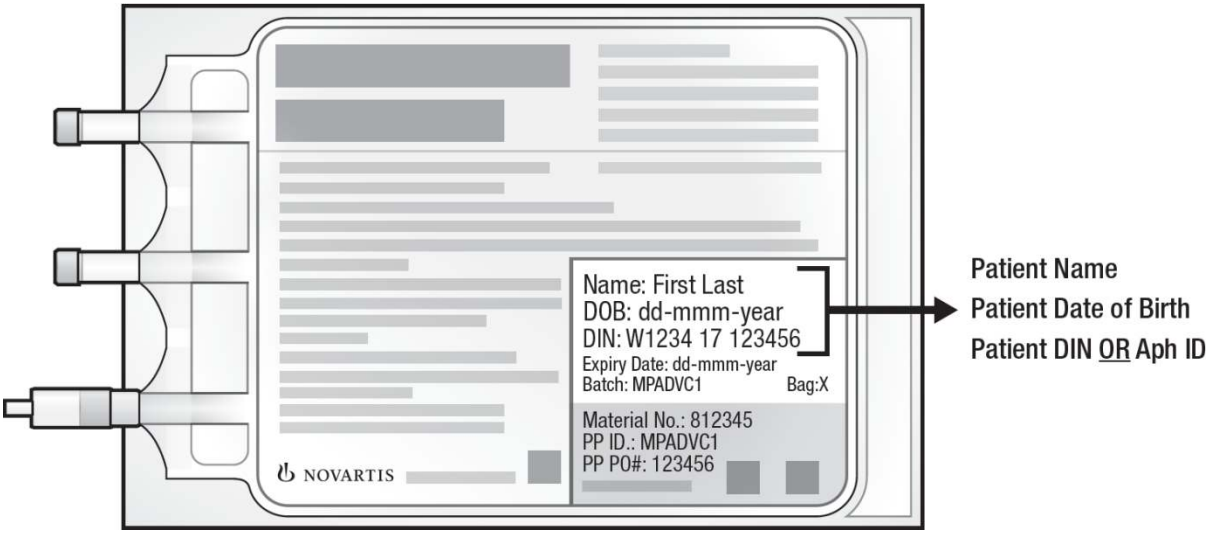
Preparation of KYMRIAH for Infusion

1. Ensure tocilizumab and emergency equipment are available prior to infusion and during the recovery period.
2. Premedicate patient with acetaminophen and diphenhydramine or another H1-antihistamine approximately 30 to 60 minutes prior to KYMRIAH infusion. Avoid prophylactic use of systemic corticosteroids, as it may interfere with the activity of KYMRIAH.

3. Confirm patient identity: Prior to KYMRIAH preparation, match the patient's identity with the patient identifiers on each KYMRIAH infusion bag(s). KYMRIAH is for autologous use only. Employ universal precautions to avoid potential transmission of infectious diseases when handling the product.

   Note: The patient identifier number may be preceded by the letters DIN or Aph ID.

Figure 1. KYMRIAH Infusion Bag



4. Inspect the infusion bag(s) for any breaks or cracks prior to thawing. If a bag is compromised, do not infuse the contents. Call Novartis at 1-844-4KYMRIAH.
5. Place the infusion bag inside a second, sterile bag in case of a leak and to protect ports from contamination.
6. Thaw each infusion bag one at a time at 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Remove bag from thawing device immediately; do not store product bag at 37°C. Once the infusion bag has been thawed and is at room temperature (20°C to 25°C), it should be infused within 30 minutes. Do not wash, spin down, and/or resuspend KYMRIAH in new media prior to infusion.
7. 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. Do not infuse KYMRIAH if clumps are not dispersed, the infusion bag is damaged or leaking, or otherwise appears to be compromised. Call Novartis at 1-844-4KYMRIAH.

Administration

8. Confirm the patient's identity with the patient identifiers on the infusion bag.
9. Administer KYMRIAH as an intravenous infusion at 10 mL to 20 mL per minute, adjusted as appropriate for smaller children and smaller volumes. The volume in the infusion bag ranges from 10 mL to 50 mL. Do NOT use a leukocyte-depleting filter. If more than one bag is being infused for the treatment dose, wait to thaw/infuse the next bag until it is determined that the previous bag is safely administered.
   - Prime the tubing prior to infusion with normal saline.
   - Infuse all contents of the infusion bag.
   - Rinse the infusion bag with 10 mL to 30 mL normal saline while maintaining a closed tubing system to assure as many cells as possible are infused into the patient.
   - Cells from all the bag(s) must be infused to complete a single dose

KYMRIAH contains human cells genetically modified with a lentivirus. Follow local biosafety guidelines applicable for handling and disposal of such products.

Monitoring

- Administer KYMRIAH at a certified healthcare facility.
- Monitor patients 2-3 times during the first week following KYMRIAH infusion at the certified healthcare facility for signs and symptoms of CRS and neurologic toxicities *[see Warnings and Precautions (5.1, 5.2)]*.
- Instruct patients to remain within proximity of the certified healthcare facility for at least 4 weeks following infusion.

2.4 Management of Severe Adverse Reactions

Cytokine Release Syndrome

Identify cytokine release syndrome (CRS) based on clinical presentation *[see Warnings and Precautions (5.1)]*. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 1.

Table 1. Treatment of CRS

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.
***CRS requiring moderate to aggressive intervention (one or more of the following)*:** – Hemodynamic 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 greater than or equal to 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.

3 DOSAGE FORMS AND STRENGTHS

Pediatric and Young Adult r/r B-cell ALL (up to 25 years of age): A single dose of KYMRIAH contains 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg of body weight for patients 50 kg and below or 0.1 to 2.5 x 10^8 CAR-positive viable T cells for patients above 50 kg, suspended in one to three patient-specific infusion bag(s) *[see How Supplied/Storage and Handling (16)]*.

Adult r/r DLBCL: A single dose of KYMRIAH contains 0.6 to 6.0 x 10^8 CAR-positive viable T cells, which may be suspended in one to three patient-specific infusion bag(s) *[see How Supplied/Storage and Handling (16)]*.

See the CoA for actual cell count. The volume in the infusion bag ranges from 10 mL to 50 mL.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome (CRS)

CRS, including fatal or life-threatening reactions, occurred following treatment with KYMRIAH. CRS occurred in 54 (79%) of the 68 pediatric and young adult patients with r/r ALL and 78 (74%) of the 106 adult patients with r/r DLBCL receiving KYMRIAH, including ≥ Grade 3 (Penn grading system[1]) in 49% of patients with r/r ALL and in 23% of patients with r/r DLBCL. The median time to onset was 3 days (range: 1-51), and in only two patients was onset after Day 10. The median time to resolution of CRS was 8 days (range: 1-36).

Of the 54 patients with r/r ALL who had CRS, 27 (50%) received tocilizumab. Seven (13%) patients received two doses of tocilizumab, 3 (6%) patients received three doses of tocilizumab, and 14 (26%) patients received addition of corticosteroids (e.g., methylprednisolone). Of the 78 patients with r/r DLBCL who had CRS, 16 (21%) received systemic tocilizumab or corticosteroids. Six (8%) patients received a single dose of tocilizumab, 10 (13%) patients received two doses of tocilizumab, and 10 (13%) patients received corticosteroids in addition to tocilizumab. Two patients with r/r DLBCL received corticosteroids for CRS without concomitant tocilizumab, and two patients received corticosteroids for persistent neurotoxicity after resolution of CRS.

Five deaths occurred within 30 days of KYMRIAH infusion. One patient with r/r ALL died with CRS and progressive leukemia, and one patient had resolving CRS with abdominal compartment syndrome, coagulopathy, and renal failure when an intracranial hemorrhage occurred. Of the 3 r/r DLBCL patients who died within 30 days of infusion, all had CRS in the setting of stable to progressive underlying disease, one of whom developed bowel necrosis. Among patients with CRS, key manifestations include fever (92% in r/r ALL and r/r DLBCL), hypotension (67% in r/r ALL; 47% in r/r DLBCL), hypoxia (20% in r/r ALL; 35% in r/r DLBCL) and tachycardia (30% in r/r ALL; 14% in r/r DLBCL). CRS may be associated with hepatic, renal, and cardiac dysfunction, and coagulopathy.

Delay the infusion of KYMRIAH after lymphodepleting chemotherapy if the patient has unresolved serious adverse reactions from preceding chemotherapies (including pulmonary toxicity, cardiac toxicity, or hypotension), active uncontrolled infection, active graft versus host disease (GVHD), or worsening of leukemia burden *[see Dosage and Administration (2.3)]*.

Ensure that two doses of tocilizumab are available on site prior to infusion of KYMRIAH. Monitor patients for signs or symptoms of CRS for at least 4 weeks after treatment with KYMRIAH. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time *[see Patient Counseling Information (17)]*. At the first sign of CRS, immediately evaluate patient for hospitalization and institute treatment with supportive care, tocilizumab and/or corticosteroids as indicated *[see Dosage and Administration (2.3, 2.4)]*.

Risk factors for severe CRS in the pediatric and young adult r/r B-cell ALL population are high pre-infusion tumor burden (greater than 50% blasts in bone marrow), uncontrolled or accelerating tumor burden following lymphodepleting chemotherapy, active infections, and/or inflammatory processes. Risk factors for developing severe CRS in adult r/r DLBCL are not known.

5.2 Neurological Toxicities

Neurological toxicities including severe or life-threatening reactions, occurred in 49 (72%) of the 68 patients with r/r ALL and 62 (58%) of the 106 patients with r/r DLBCL following treatment with KYMRIAH, including ≥ Grade 3 in 21% of patients with r/r ALL and 18% of patients with r/r DLBCL. Among patients who had a neurological toxicity, 88% occurred within 8 weeks following KYMRIAH infusion.

Median time to the first event was 6 days from infusion (range: 1-359), and the median duration was 6 days for patients with r/r ALL and 14 days for patients with r/r DLBCL. Resolution occurred within 3 weeks in 79% of patients with r/r ALL and 61% of patients with r/r DLBCL. Encephalopathy lasting up to 50 days was noted.

The onset of neurological toxicity can be concurrent with CRS, following resolution of CRS or in the absence of CRS.

The most common neurological toxicities observed with KYMRIAH include headache (37% in r/r ALL; 21% in r/r DLBCL), encephalopathy (34% in r/r ALL; 16% in r/r DLBCL), delirium (21% in r/r ALL; 6% in r/r DLBCL), anxiety (13% in r/r ALL; 9% in r/r DLBCL), sleep disorders (10% in r/r ALL; 9% in r/r DLBCL), dizziness (6% in r/r ALL; 11% in r/r DLBCL), tremor (9% in r/r ALL; 7% r/r DLBCL) and peripheral neuropathy (4% in r/r ALL; 8% in r/r DLBCL). Other manifestations included seizures, mutism and aphasia.

Monitor patients for neurological events and exclude other causes for neurological symptoms. Provide supportive care as needed for KYMRIAH-associated neurological events.

5.3 KYMRIAH REMS to Mitigate Cytokine Release Syndrome and Neurological Toxicities

Because of the risk of CRS and neurological toxicities, KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS *[see Boxed Warning, Warnings and Precautions (5.1, 5.2)]*. The required components of the KYMRIAH REMS are:

- Healthcare facilities that dispense and administer KYMRIAH must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of two doses of tocilizumab are available for each patient for administration within 2 hours after KYMRIAH infusion, if needed for treatment of CRS.
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer KYMRIAH are trained about the management of CRS and neurological toxicities.

Further information is available at www.kymriah-rems.com or 1-844-4KYMRIAH.

5.4 Hypersensitivity Reactions

Allergic reactions may occur with infusion of KYMRIAH. Serious hypersensitivity reactions, including anaphylaxis, may be due to the dimethyl sulfoxide (DMSO) or dextran 40 in KYMRIAH.

5.5 Serious Infections

Infections, including life-threatening or fatal infections, occurred in 95 (55%) of 174 patients with r/r ALL or r/r DLBCL after KYMRIAH infusion. Fifty eight patients (33%) experienced Grade ≥ 3 infections, including fatal infections in 2 patients (3%) with r/r ALL and 1 patient (1%) with r/r DLBCL. Prior to KYMRIAH infusion, infection prophylaxis should follow local guidelines. Patients with active uncontrolled infection should not start KYMRIAH treatment until the infection is resolved. Monitor patients for signs and symptoms of infection after treatment with KYMRIAH and treat appropriately *[see Dosage and Administration (2.3)]*.

Febrile neutropenia (≥ Grade 3) was also observed in 37% of patients with r/r ALL and 17% of patients with r/r DLBCL after KYMRIAH infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids and other supportive care as medically indicated.

Viral Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs directed against B cells.

Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing.

5.6 Prolonged Cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and KYMRIAH infusion.

In the ELIANA study (Study 1), ≥ Grade 3 cytopenias not resolved by Day 28 following KYMRIAH treatment included neutropenia (40%), and thrombocytopenia (27%) among 52 responding patients. At 56 days following KYMRIAH, 17% and 12% of responding patients had ≥ Grade 3 neutropenia or thrombocytopenia respectively.

In the JULIET study (Study 2), ≥ Grade 3 cytopenias not resolved by Day 28 following KYMRIAH treatment included thrombocytopenia (40%) and neutropenia (25%) among 106 treated patients.

Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, particularly GM-CSF, are not recommended during the first 3 weeks after KYMRIAH infusion or until CRS has resolved.

5.7 Hypogammaglobulinemia

Hypogammaglobulinemia and agammaglobulinemia (IgG) related to B-cell aplasia can occur in patients with a complete remission (CR) after KYMRIAH infusion.

Hypogammaglobulinemia was reported in 43% of patients treated with KYMRIAH for r/r ALL and 14% of patients with r/r DLBCL *[see Clinical Pharmacology (12.3)]*.

Monitor immunoglobulin levels after treatment with KYMRIAH and manage using infection precautions, antibiotic prophylaxis and immunoglobulin replacement standard guidelines.

Immunization with Live Vaccine

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

Pregnant women who have received KYMRIAH may have hypogammaglobulinemia. Assess immunoglobulin levels in newborns of mothers treated with KYMRIAH.

5.8 Secondary Malignancies

Patients treated with KYMRIAH may develop secondary malignancies or recurrence of their cancer. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Novartis Pharmaceuticals Corporation at 1-844-4KYMRIAH to obtain instructions on patient samples to collect for testing.

5.9 Effects on Ability to Drive and Use Machines

Due to the potential for neurological events, including altered mental status or seizures, patients receiving KYMRIAH are at risk for altered or decreased consciousness or coordination in the 8 weeks following KYMRIAH infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label:

- Cytokine Release Syndrome *[see Warnings and Precautions (5.1)]*
- Neurological Toxicities *[see Warnings and Precautions (5.2)]*
- Infections and Febrile Neutropenia *[see Warnings and Precautions (5.5)]*
- Prolonged Cytopenias *[see Warnings and Precautions (5.6)]*
- Hypogammaglobulinemia *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described in the WARNINGS AND PRECAUTIONS and in this section reflect exposure to KYMRIAH in two non-randomized, single-arm studies in which 68 pediatric and young adult patients with relapsed/refractory (r/r) B-cell ALL (ELIANA Study) and 106 adults with r/r diffuse large B-cell lymphoma (JULIET Study) received a single dose of CAR-positive viable T cells.

Pediatric and Young Adult r/r B-cell Acute Lymphoblastic Leukemia (ALL) (up to 25 years of age)

Based on a recommended dose which was weight-based, all 68 patients in the ELIANA study (Study 1) received a single intravenous dose of KYMRIAH *[see Clinical Studies (14.1)]*. The most common adverse reactions (> 20%) were cytokine

release syndrome (79%), hypogammaglobulinemia (43%), infections-pathogen unspecified (41%), pyrexia (40%), decreased appetite (37%), headache (37%), encephalopathy (34%), hypotension (31%), bleeding episodes (31%), tachycardia (26%), nausea (26%), diarrhea (26%), vomiting (26%), viral infectious disorders (26%), hypoxia (24%), fatigue (25%), acute kidney injury (24%), edema (21%), cough (21%), and delirium (21%).

The adverse reactions with greater or equal to 10% incidence for any Grade are summarized in Table 2.

Table 2. Selected Adverse Reactions Anytime After Infusion (≥ 10%) Following Treatment with KYMRIAH in Pediatric and Young Adult r/r B-cell ALL (N = 68)

Adverse Reaction	All Grades (%)	Grades 3 or Higher (%)
Blood and lymphatic system disorders		
Febrile Neutropenia	37	37
Cardiac disorders		
[a]Tachycardia	26	4
Gastrointestinal disorders		
Nausea	26	3
Diarrhea	26	1
Vomiting	26	1
Constipation	18	0
[b]Abdominal pain	16	3
General disorders and administration site conditions		
Pyrexia	40	15
[c]Fatigue	25	0
[d]Edema	21	1
Chills	10	0
[e]Pain	18	3
Immune system disorders		
Cytokine release syndrome	79	49
[f]Hypogammaglobulinemia	43	7
Infections and infestations		
Infections-pathogen unspecified	41	16
Viral infectious disorders	26	18
Bacterial infectious disorders	19	13
Fungal infectious disorders	13	7
Investigations		
International normalized ratio increased	13	0
Metabolism and nutrition disorders		
Decreased appetite	37	15
Fluid overload	10	7
Musculoskeletal and connective tissue disorders		
Myalgia	15	0
Arthralgia	12	1
Back pain	10	3
Nervous system disorders		
[g]Headache	37	3
[h]Encephalopathy	34	10

Adverse Reaction	All Grades (%)	Grades 3 or Higher (%)
Psychiatric disorders		
[i]Delirium	21	4
Anxiety	13	3
[j]Sleep disorders	10	0
Renal and urinary disorders		
[k]Acute kidney injury	24	15
Respiratory, thoracic and mediastinal disorders		
Hypoxia	24	18
[l]Cough	21	0
[m]Dyspnea	16	12
Pulmonary edema	16	10
Tachypnea	12	6
Pleural effusion	10	4
Nasal congestion	10	0
Skin and subcutaneous tissue disorders		
[n]Rash	16	1
Vascular disorders		
Hypotension	31	22
Hypertension	19	6

[a]*Tachycardia includes tachycardia and sinus tachycardia.*
[b]*Abdominal pain includes abdominal pain, abdominal pain upper.*
[c]*Fatigue includes fatigue and malaise.*
[d]*Edema includes face edema, generalised edema, localised edema, edema peripheral.*
[e]*Pain includes pain and pain in the extremity.*
[f]*Hypogammaglobulinemia includes hypogammaglobulinemia, immunoglobulins decreased, blood immunoglobulin G decreased, blood immunoglobulin A decreased, blood immunoglobulin M decreased.*
[g]*Headache includes headache and migraine.*
[h]*Encephalopathy includes encephalopathy, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, lethargy, mental status changes, somnolence, and automatism.*
[i]*Delirium includes delirium, agitation, hallucination, hallucination visual, irritability, restlessness.*
[j]*Sleep disorders includes sleep disorder, insomnia and nightmare.*
[k]*Acute kidney injury includes acute kidney injury, anuria, azotemia, renal failure, renal tubular dysfunction, renal tubular necrosis, and blood creatinine increased.*
[l]*Cough includes cough and productive cough.*
[m]*Dyspnea includes dyspnea and respiratory distress, respiratory failure.*
[n]*Rash includes rash, rash maculo-papular, rash papular, and rash pruritic.*

Additional important adverse reactions that did not meet the threshold criteria for inclusion in Table 2 were:

Blood and lymphatic system disorders: disseminated intravascular coagulation (9%), histiocytosis lymphocytic hemophagocytosis (7%), coagulopathy (6%), Grade 3 and Grade 4 hypofibrinogenemia with Grade 3 and 4 CRS (16%)

Cardiac Disorders: cardiac arrest (4%), cardiac failure (7%)

Gastrointestinal disorders: abdominal compartment syndrome (1%)

General disorders and administration site conditions: multiple organ dysfunction syndrome (3%)

Immune system disorders: graft versus host disease (1%)

Investigations: activated partial thromboplastin time prolonged (6%)

Nervous System: tremor (9%), dizziness (6%), seizure (3%), speech disorder[a] (3%), motor dysfunction[b] (1%)

Respiratory, thoracic, and mediastinal disorders: respiratory distress (6%), respiratory failure (6%)**,** acute respiratory distress syndrome (4%), oropharyngeal pain (6%)

Metabolism and nutrition disorders: tumor lysis syndrome (6%)

Vascular disorders: capillary leak syndrome (3%), thrombosis (3%)

Eye disorders: Visual impairment (3%)

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[a]*Speech disorder includes aphasia and dysarthria.*
[b]*Motor dysfunction includes muscle spasms.*

Laboratory Abnormalities

Selected laboratory abnormalities worsening from baseline Grade 0-2 to Grade 3-4 are shown in Table 3.

Table 3. Selected Other Laboratory Abnormalities Worsening (> 10%) from Baseline Grade 0-2 to Grade 3-4 Following Treatment with KYMRIAH in Pediatric and Young Adult r/r B-cell ALL based on CTCAE[a] (N = 68)

Laboratory Abnormality	Grade 3 or 4 (%)
Increased Aspartate Aminotransferase	28
Hypokalemia	27
Increased Alanine Aminotransferase	21
Increased bilirubin	21
Hypophosphatemia	19

[a]CTCAE = Common Terminology Criteria for Adverse Events version 4.03

All patients experienced neutropenia, anemia and thrombocytopenia. See Table 4 for the incidences of ≥ Grade 3 prolonged thrombocytopenia and prolonged neutropenia in responding patients.

Table 4. Prolonged Cytopenias Following Treatment with KYMRIAH in Pediatric and Young Adult r/r B-cell ALL

Prolonged Cytopenia	N = 52 (%)	N = 52 (%)
	Day 28	Day 56
Prolonged neutropenia[a]	40	17
Prolonged thrombocytopenia[a]	27	12

[a] ≥ Grade 3 observed within 14 days after Day 28 or Day 56 in responding patients

Adult r/r Diffuse Large B-cell Lymphoma (DLBCL)

In the JULIET study (Study 2) 106 adults with r/r DLBCL received a single intravenous dose of KYMRIAH *[see Clinical Studies (14.2)]*. The most common adverse reactions (incidence > 20%) were cytokine release syndrome, infections-pathogen unspecified, diarrhea, nausea, pyrexia, fatigue, hypotension, edema and headache.

The study population characteristics were: median age of 56 years (range: 22 to 76 years), 79% DLBCL; a median of 3 prior lines of therapy (range: 1-6), 49% had a prior autologous hematopoietic stem cell transplantation, and 33% had received prior radiation therapy. Ninety-nine patients (93%) received lymphodepleting chemotherapy prior to KYMRIAH, that included fludarabine (n = 77) or bendamustine (n = 22).

The adverse reactions with greater than or equal to 10% incidence for any Grade are summarized in Table 5 below.

Table 5. Selected Adverse Reactions Anytime After Infusion Reported in ≥ 10% Following Treatment with KYMRIAH in Adult r/r DLBCL (N = 106)

Adverse Reaction	All Grades (%)	Grades 3 or Higher (%)
Blood and lymphatic system disorders		
Febrile Neutropenia	17	17
Cardiac disorders		
[a]Tachycardia	13	3
Gastrointestinal disorders		
Diarrhea	31	1
Nausea	27	1
Constipation	16	1
General disorders and administration site conditions		
Pyrexia	34	6
[b]Fatigue	26	7
[c]Edema	23	2

Adverse Reaction	All Grades (%)	Grades 3 or Higher (%)
[d]Pain	15	3
Chills	13	0
Immune system disorders		
Cytokine release syndrome	74	23
[e]Hypogammaglobulinemia	14	4
Infections and infestations		
Infections-pathogen unspecified	42	25
Investigations		
Weight decreased	11	3
Metabolism and nutrition disorders		
Decreased appetite	12	4
Musculoskeletal and connective tissue disorders		
Arthralgia	10	0
Nervous system disorders		
[f]Headache	21	0
[g]Encephalopathy	16	11
[h]Dizziness	11	1
Renal and Urinary Disorders		
[i]Acute kidney injury	17	6
Respiratory, thoracic and mediastinal disorders		
[j]Cough	19	0
[k]Dyspnea	18	6
Vascular disorders		
[l]Hypotension	26	8

[a]*Tachycardia includes tachycardia and sinus tachycardia.*
[b]*Fatigue includes fatigue and malaise.*
[c]*Edema includes face edema, generalised edema, localized edema, edema peripheral, peripheral swelling.*
[d]*Pain includes pain and pain in the extremity.*
[e]*Hypogammaglobulinemia includes blood immunoglobulin G decreased, immunoglobulins decreased and hypogammaglobulinemia.*
[f]*Headache includes headache and migraine.*
[g]*Encephalopathy includes encephalopathy, cognitive disorder, confusional state, disturbance in attention, lethargy, mental status changes, somnolence, memory impairment, metabolic encephalopathy and thinking abnormal.*
[h]*Dizziness includes dizziness, presyncope, and syncope.*
[i]*Acute kidney injury includes acute kidney injury and blood creatinine increased.*
[j]*Cough includes cough, productive cough, and upper-airway cough syndrome.*
[k]*Dyspnea includes dyspnea, dyspnea exertional, respiratory distress, and respiratory failure.*
[l]*Hypotension includes hypotension and orthostatic hypotension.*

Additional important adverse reactions that did not meet the threshold criteria for inclusion in Table 5 were*:*

Blood and lymphatic system disorders: disseminated intravascular coagulation (3%), pancytopenia (2%), histiocytosis hematophagic (1%)

Cardiac Disorders: arrhythmia[a] (6%)

Gastrointestinal disorders: vomiting (9%), abdominal pain[b] (9%), anal incontinence (1%)

General disorders and administration site conditions: asthenia (7%), multiple organ dysfunction syndrome (3%)

Infections and infestations: fungal infectious disorders (9%), viral infectious disorders (9%), bacterial infectious disorders (9%)

Musculoskeletal and connective tissue disorders: myalgia (7%), back pain (6%)

Nervous System: peripheral neuropathy[c] (8%), motor dysfunction[d] (6%), speech disorder[e] (3%), seizure[f] (3%), ischemic cerebral infarction (1%), tremor (7%), ataxia (2%)

Psychiatric disorders: anxiety (9%), delirium[g] (6%), sleep disorders[h] (9%)

Respiratory, thoracic, and mediastinal disorders: hypoxia (8%), oropharyngeal pain[i] (8%), pleural effusion (5%) pulmonary edema[j] (3%)

Metabolism and nutrition disorders: fluid overload (3%), tumor lysis syndrome (1%)

Vascular disorders: thrombosis[k] (7%), hypertension (2%), capillary leak syndrome (1%)

Skin and subcutaneous tissue disorders: rash[l] (8%), dermatitis[m] (4%)

Eye disorders: visual impairment[n] (7%)

[a] *Arrhythmia includes atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles.*
[b] *Abdominal pain includes abdominal pain and abdominal pain upper.*
[c] *Peripheral Neuropathy includes paraethesia,hypoaesthesia, hyperaesthesia,peripheral sensory neuropathy, and neuropathy peripheral.*
[d] *Motor dysfunction includes muscle spasms, muscle twitching, myoclonus and myopathy.*
[e] *Speech disorder includes speech disorder, aphasia.*
[f] *Seizure includes PTs seizure and status epilepticus.*
[g] *Delirium includes delirium, agitation, and irritability.*
[h] *Sleep disorders includes sleep disorder, insomnia and nightmare.*
[i] *Oropharyngeal pain includes oral pain and oropharyngeal pain.*
[j] *Pulmonary edema includes acute pulmonary edema and pulmonary edema.*
[k] *Thrombosis includes deep vein thrombosis, embolism, pulmonary embolism, thrombosis, vena cava thrombosis, and venous thrombosis.*
[l] *Rash includes rash, rash maculo-papular, rash papular and rash pruritic.*
[m] *Dermatitis includes dermatitis, dermatitis acneiform and dermatitis contact.*
[n] *Visual impairment includes vision blurred and visual impairment.*

Laboratory Abnormalities

Selected laboratory abnormalities worsening from baseline Grade 0-2 to Grade 3-4 are shown in Table 6.

Table 6. Grade 3 or 4 Laboratory Abnormalities occurring in > 10% of Patients Following KYMRIAH Infusion in Adult r/r DLBCL Patients Based on CTCAE[a] N = 106

Laboratory Parameter	Grade 3 or 4 (%)
Hematology	
Lymphopenia	94
Neutropenia	81
Leukopenia	77
Anemia	58
Thrombocytopenia	54
Biochemistry	
Hypophosphatemia	24
Hypokalemia	12
Hyponatremia	11

[a] CTCAE = Common Terminology Criteria for Adverse Events version 4.03

6.2 Immunogenicity

In clinical studies, humoral immunogenicity of KYMRIAH was measured by determination of anti-murine CAR19 antibodies (anti-mCAR19) in serum pre- and post-administration. The majority of patients, 86% in ELIANA (Study 1) and 91.4% in JULIET (Study 2) tested positive for pre-dose anti-mCAR19 antibodies prior to KYMRIAH infusion;

Treatment induced anti-mCAR19 antibodies were detected in 5% of the patients in JULIET. However, the preexisting and treatment-induced antibodies were not associated with an impact on clinical response and did not have an impact on the initial expansion and persistence of KYMRIAH. Persistence of KYMRIAH was similar between patients with positive post-infusion anti-mCAR19 antibodies compared with patients with negative post-infusion anti-mCAR19 antibodies. There is no evidence that the presence of preexisting and treatment-induced anti-mCAR19 antibodies impact the safety or effectiveness of KYMRIAH.

T cell immunogenicity responses were not observed in adult r/r DLBCL patients.

7 DRUG INTERACTIONS

HIV and the lentivirus used to make KYMRIAH have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid test (NATs) tests may yield false-positive results in patients who have received KYMRIAH.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with KYMRIAH use in pregnant women. No animal reproductive and developmental toxicity 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 the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia. Therefore, KYMRIAH is not recommended for women who are pregnant, and pregnancy after KYMRIAH administration should be discussed with the treating physician. Report pregnancies to Novartis Pharmaceuticals Corporation at 1-888-669-6682.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of KYMRIAH in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KYMRIAH and any potential adverse effects on the breastfed infant from KYMRIAH or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy status of females with reproductive potential should be verified. Sexually-active females of reproductive potential should have a pregnancy test prior to starting treatment with KYMRIAH.

Contraception

See the prescribing information for fludarabine and cyclophosphamide 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.

Infertility

There are no data on the effect of KYMRIAH on fertility.

8.4 Pediatric Use

The safety and efficacy of KYMRIAH have been established in pediatric patients with r/r B-cell ALL. Use of KYMRIAH is supported by a single-arm trial *[see Clinical Studies (14.1)]* that included 52 pediatric patients with r/r B-cell precursor ALL in the following age groups: 33 children (age 3 years to less than 12 years) and 19 adolescents (age 12 years to less

than 17 years). No differences in efficacy or safety were observed between the different age subgroups or in comparison to the young adults in the trial.

The safety and efficacy of KYMRIAH in pediatric patients with relapsed or refractory DLBCL has not been established.

8.5 Geriatric Use

The safety and effectiveness of KYMRIAH have not been established in geriatric patients with r/r B-cell ALL. Clinical studies of KYMRIAH did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

11 DESCRIPTION

KYMRIAH (tisagenlecleucel) is a CD19-directed genetically modified autologous T cell immunotherapy comprised of autologous T cells that are genetically modified using a lentiviral vector to encode an anti-CD19 chimeric antigen receptor (CAR). The CAR is comprised of a murine single-chain antibody fragment (scFv) specific for CD19, followed by a CD8 hinge and transmembrane region that is fused to the intracellular signaling domains for 4-1BB (CD137) and CD3 zeta.

KYMRIAH is prepared from the patient's peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure. The mononuclear cells are enriched for T cells, then transduced with the lentiviral vector containing the anti-CD19 CAR transgene, and activated with anti-CD3/CD28 antibody coated beads. The transduced T cells are expanded in cell culture, washed, and formulated into a suspension, which then is cryopreserved. The product must pass a sterility test before release for shipping as a frozen suspension in a patient-specific infusion bag(s). The product is thawed prior to administration *[see Dosage and Administration (2.3), How Supplied/Storage and Handling (16)]*. The thawed product is a colorless to slightly yellow suspension of cells.

In addition to T cells, other cell populations, including monocytes, NK cells, and B cells, may be present. The formulation contains 31.25% (v/v) of Plasma-Lyte A, 31.25% (v/v) of 5% Dextrose/0.45% sodium chloride, 10 % Dextran 40 (LMD)/5% Dextrose, 20% (v/v) of 25% Human Serum Albumin (HSA), and 7.5% (v/v) Cryoserv® dimethylsulfoxide (DMSO).

Pediatric and Young Adult r/r B-cell ALL: A single dose of KYMRIAH may contain up to 2.5 x 10^8 CAR-positive viable T cells provided in one to three patient-specific infusion bag(s). Based on the patient's weight reported at the time of leukapheresis, one of two possible dose ranges will be prepared for the patient:

- For patients 50 kg or less: 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg body weight
- For patients above 50 kg: 0.1 to 2.5 x 10^8 CAR-positive viable T cells

Adult r/r DLBCL: A single dose of KYMRIAH may contain 0.6 to 6.0 x 10^8 CAR-positive viable T cells provided in one to three patient-specific infusion bag(s).

The actual number of CAR-positive T cells in the product is reported on the Certificate of Analysis (CoA) that is shipped with KYMRIAH. The volume of CAR-positive viable T cells in an infusion bag ranges from 10 mL to 50 mL.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

KYMRIAH is a CD19-directed genetically modified autologous T cell immunotherapy which involves reprogramming a patient's own T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19-expressing malignant and normal cells. The CAR is comprised of a murine single-chain antibody fragment which recognizes CD19 and is fused to intracellular signaling domains from 4-1BB (CD137) and CD3 zeta. The CD3 zeta component is critical for initiating T-cell activation and antitumor activity, while 4-1BB enhances the expansion and persistence of KYMRIAH. Upon binding to CD19-expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, target cell elimination, and persistence of the KYMRIAH cells.

12.3 Pharmacokinetics/Cellular Kinetics

Following infusion, KYMRIAH exhibited an initial rapid expansion followed by a bi-exponential decline in both pediatric and young adult relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) patients, and adult relapsed/refractory diffuse large B-cell lymphoma patients.

A summary of pharmacokinetic parameters of KYMRIAH is provided in Table 7 below**.**

Table 7. Pharmacokinetic Parameters of KYMRIAH in Pediatric and Young Adult r/r B-cell ALL and Adult r/r DLBCL

Parameter	Summary Statistics	Pediatric ALL Responding Patients	Pediatric ALL Non-Responding Patients	r/r DLBCL Responding Patients (CR and PR)	r/r DLBCL Non-Responding Patients (SD/PD/Unknown)
		N = 62	N = 8	N = 34	N = 34
C_{max} (copies/mcg)	Geometric mean (CV%), n	34,700 (155.4), 61	20,000 (71.6%), 7	5210 (256.5), 33	6450 (408.2), 32
T_{max} (day)	Median [min; max], n	9.91 [0.008; 27], 61	20.0 [0.03; 62.7], 7	9.83 [5.73, 16.8], 33	8.39 [3.04, 27.7], 32
$AUC_{0\text{-}28d}$ (copies/mcg*day)	Geometric mean (CV%), n	318,000 (177.8), 61	156,000 (99.4), 6	58200 (165.1), 30	75800 (292.3), 25
$T_{½}$ (day)	Geometric mean (CV%), n	16.8 (155.9), 54	2.52 (171.9), 3	45.3 (157.7), 21	13.6 (167.0), 22

‡A total of 7 patients had an early T_{max} (< 0.03 days), the next lowest T_{max} occurred at 5.7 days. Early T_{max} may not be representative of the true maximal expansion, but rather representative of the amount of transgene present in the catheter from which sample was collected.

Description of Pharmacokinetics in Pediatric and Young Adult r/r B-cell ALL (up to 25 years of age)

The C_{max} and $AUC_{0\text{-}28d}$ were approximately 2-fold higher in CR/CRi patients compared with non-responding (NR) patients.

KYMRIAH was present in the blood as well as bone marrow and was measurable beyond 2 years. Blood to bone marrow partitioning suggested that KYMRIAH distribution in bone marrow was 44% of that present in blood at Day 28 while at Months 3 and 6 KYMRIAH distributed at 67% and 69%, respectively, indicating high distribution to bone marrow. Children < 10 years and between 10-18 years of age had 1.5- to 2-fold higher C_{max} and $AUC_{0\text{-}28d}$ than adults. Due to small sample size and high variability, it is difficult to assess the impact of age on the pharmacokinetics of KYMRIAH.

Description of Pharmacokinetics in Adult r/r DLBCL

The C_{max} and $AUC_{0\text{-}28d}$ were similar between responding and non-responding (NR) patients.

KYMRIAH was present in adult r/r DLBCL patients up to 18 months in peripheral blood and up to 9 months in the bone marrow for patients having a complete response. The median time of maximal expansion of transgene levels (T_{max}) in peripheral blood occurred at 9-10 days in both responding and non-responding patients.

Tocilizumab and Corticosteroid use

Some patients required tocilizumab and corticosteroids for the management of CRS. KYMRIAH continues to expand and persist following tocilizumab administration. Patients who have higher expansion tended to have higher CRS Grades *[see Warnings and Precautions (5.1)]*.

Pediatric and young adult r/r B-cell ALL patients (n = 18) treated with tocilizumab had 265% and 183% higher KYMRIAH $AUC_{0\text{-}28d}$ and C_{max}, respectively, as compared to patients (n = 44) who did not receive tocilizumab. In addition, patients who received corticosteroids had 89% higher $AUC_{0\text{-}28d}$ compared with patients who did not receive corticosteroids.

Adult /r/r DLBCL patients treated with tocilizumab (N = 15) had 199% (n = 11) and 257% (n = 13) higher KYMRIAH $AUC_{0\text{-}28d}$ and C_{max}, respectively, as compared to patients (N = 90) who did not receive tocilizumab. In addition, patients who received corticosteroids (N = 11) had 122% and 161% higher $AUC_{0\text{-}28d}$ and C_{max}, respectively, as compared with patients who did not receive corticosteroids (N = 94). Hepatic and renal impairment studies of KYMRIAH were not conducted.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Genotoxicity assays and carcinogenicity assessment in rodent models were not performed for KYMRIAH. *In vitro* expansion studies with transduced T cells (KYMRIAH) from healthy donors and patients showed no evidence for transformation and/or immortalization of T cells. *In vivo* studies in immunocompromised mice did not show signs of abnormal cell growth or signs of clonal cell expansion for up to 7 months after cell injection. A genomic insertion site analysis was performed on KYMRIAH products from 14 individual donors (12 patients and 2 healthy volunteers). There was no evidence for preferential integration near genes of concern, or preferential outgrowth of cells harboring integration sites of concern

No studies on the effects of KYMRIAH on fertility have been conducted.

14 CLINICAL STUDIES

14.1 Relapsed or Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL)

The efficacy of KYMRIAH in pediatric and young adults with r/r B-cell precursor ALL was evaluated in an open-label, multicenter single-arm trial (ELIANA, NCT02228096). In total, 107 patients were screened, 88 were enrolled, 68 were treated, and 63 were evaluable for efficacy. Nine percent of the enrolled patients did not receive the product due to manufacturing failure. The 63 evaluable patients included 35 males and 28 females of median age 12 years (range: 3-23 years). Seventy-three percent of patients were White, 10% were Asian, and 17% were of other races. Six (10%) had primary refractory disease, 30 (48%) had one prior stem cell transplantation, 5 patients (8%) had two stem cell transplantations. Treatment consisted of lymphodepleting chemotherapy (fludarabine 30 mg/m^2 daily for 4 days and cyclophosphamide 500 mg/m^2 daily for 2 days) followed by a single dose of KYMRIAH. Of the 22 patients who had a WBC count < 1000/μL, 20 received lymphodepleting chemotherapy prior to KYMRIAH while 2 received KYMRIAH infusion without lymphodepleting chemotherapy. Fifty-three patients received bridging chemotherapy between time of enrollment and lymphodepleting chemotherapy.

The efficacy of KYMRIAH was established on the basis of complete remission (CR) within 3 months after infusion, the duration of CR, and proportion of patients with CR and minimal residual disease (MRD) < 0.01% by flow cytometry (MRD-negative) (Table 8). Among the 63 infused patients, 52 (83%) achieved CR/CRi, all of which were MRD-negative. With a median follow-up of 4.8 months from response, the median duration of CR/CRi was not reached (range: 1.2 to 14.1+ months). Median time to onset of CR/CRi was 29 days with onset of CR/CRi between 26 and 31 days for 50/52 (96%) responders. The stem cell transplantation rate among those who achieved CR/CRi was 12% (6/52). Table 8 shows the efficacy results from this study.

Table 8. Efficacy Results in Pediatric and Young Adult Patients with r/r B-cell ALL

Results	**N = 63**
CR/CRi[1,2] 95% CI	52 (83%) (71%, 91%) p < 0.0001
CR[3]	40 (63%)
CRi[4]	12 (19%)
CR or CRi with MRD-negative bone marrow[5,6] 95% CI	52 (83%) (71%, 91%) p < 0.0001
Duration of Remission[7]	**N = 52**
Median (months)	Not reached
95% CI	(7.5, NE[8])

[1]CR/CRi was calculated based on all patients who received KYMRIAH and completed at least 3 months follow-up, or discontinued earlier prior to the data cut-off. Requires remission status to be maintained for at least 28 days without clinical evidence of relapse.
[2] The null hypothesis of CR/CRi less than or equal to 20% was rejected.
[3]CR (complete remission) was defined as less than 5% of blasts in the bone marrow, no evidence of extramedullary disease, and full recovery of peripheral blood counts (platelets greater than 100,000/microliter and absolute neutrophil counts [ANC] greater than 1,000/microliter) without blood transfusion.
[4]CRi (complete remission with incomplete blood count recovery) was defined as less than 5% of blasts in the bone marrow, no evidence of extramedullary disease, and without full recovery of peripheral blood counts with or without blood transfusion.
[5]MRD (minimal residual disease) negative was defined as MRD by flow cytometry less than 0.01%.
[6]The null hypothesis of MRD-negative remission rate less than or equal to 15% was rejected.
[7]DOR (duration of remission) was defined as time since onset of CR or CRi to relapse or death due to underlying cancer, whichever is earlier, censoring for new cancer therapy including stem cell transplantation (N = 52).
[8]Not Estimable.

14.2 Adult Relapsed or Refractory (r/r) Diffuse Large B-cell Lymphoma (DLBCL)

The efficacy and safety of KYMRIAH was evaluated in an open-label, multicenter, single-arm trial (JULIET; NCT02445248). Eligible patients were ≥ 18 years of age with relapsed or refractory DLBCL, who received ≥ 2 lines of chemotherapy, including rituximab and anthracycline, or relapsed following autologous hematopoietic stem cell transplantation (HSCT). The study excluded patients with active central nervous system malignancy, prior allogenic HSCT, an ECOG performance status ≥ 2, a creatinine clearance < 60, alanine aminotransferase > 5 times normal, cardiac ejection fraction < 45%, or absolute lymphocyte concentration less than 300/μL.

Following 2 to 11 days after completion of lymphodepleting (LD) chemotherapy consisting of either fludarabine (25 mg/m^2 i.v. daily for 3 days) and cyclophosphamide (250 mg/m^2 i.v. daily for 3 days starting with the first dose of fludarabine) or bendamustine (90 mg/m^2 i.v. daily for 2 days), KYMRIAH was administered as a single intravenous infusion. Bridging chemotherapy between leukapheresis and LD chemotherapy was permitted to control disease burden. LD chemotherapy could be omitted if the white blood cell count was < 1000 cells/μL. The major efficacy outcome measures were objective response rate per Lugano criteria [2014] as assessed by an independent review committee and duration of response.

Of the 160 patients enrolled, 106 patients received tisagenlecleucel, including 92 patients who received product manufactured in the U.S. and were followed for at least 3 months or discontinued earlier. Eleven out of 160 patients enrolled did not receive tisagenlecleucel due to manufacturing failure. Thirty-eight other patients did not receive tisagenlecleucel, primarily due to death (n = 16), physician decision (n = 16), and adverse events (n = 3).

Of the 92 patients receiving KYMRIAH, 90% received physician's choice of bridging chemotherapy in the interval between start of screening and KYMRIAH infusion, among whom the median number of bridging chemotherapy regimens was 1 (range: 1 to 5) with 83% of patients receiving ≤ 2 regimens. A retrospectively identified sub-group of 68 patients was evaluable for the major efficacy outcome measures. Patients included in this sub-group had either had no bridging chemotherapy, or had imaging that showed measurable disease after completion of bridging chemotherapy, prior to KYMRIAH infusion. Of the 24 patients not included, 8 had no evidence of disease at baseline prior to KYMRIAH infusion, 15 did not have baseline imaging following bridging chemotherapy, and 1 was excluded because of initial misclassification of a neuroendocrine tumor as DLBCL.

Among the efficacy evaluable population of 68 patients, the baseline characteristics were: median age 56 years (range: 22 to 74 years); 71% male; 90% White, 4% Asian, and 3% Black or African American; 78% had primary DLBCL not otherwise specified (NOS) and 22% had DLBCL following transformation from follicular lymphoma, of whom 17% were identified as high grade; and 44% had undergone prior autologous HSCT. The median number of prior therapies was 3 (range: 1 to 6), 56% had refractory disease and 44% relapsed after their last therapy. Ninety percent of patients received lymphodepleting chemotherapy (66% of patients received fludarabine and 24% received bendamustine) and 10% did not receive any LD chemotherapy. The median time from leukapheresis and cryopreservation to KYMRIAH infusion was 113 days (range: 47 to 196 days). The median dose was 3.5×10^8 CAR-positive viable T cells (range: 1.0 to 5.2×10^8 cells). Seventy-three percent of patients received KYMRIAH in the inpatient setting.

Efficacy was established on the basis of complete response (CR) rate and duration of response (DOR), as determined by an independent review committee (Table 9 and Table 10). The median time to first response to KYMRIAH (CR or PR) was 0.9 months (range: 0.7 to 3.3 months). The median duration of response was not reached. Response durations were longer in patients who achieved CR, as compared to patients with a best response of partial response (PR) (Table 12). Of

the 22 patients who experienced a CR, 9 achieved this status by 1 month, 12 more by month 3, and the last by month 6 after KYMRIAH infusion.

Table 9. Response Rates in Relapsed or Refractory DLBCL in the JULIET Study

Response Rate	N = 68
Overall Response Rate (ORR) (CR+PR), n (%) (95% CI)	34 (50 %) (37.6%, 62.4%)
Complete Response Rate n (%) (95% CI)	22 (32%) (21.5%, 44.8%)
Partial Response Rate n (%) (95% CI)	12 (18%) (9.5%, 28.8%)

Table 10. Duration of Response[a] (Months) in Relapsed or Refractory DLBCL in the JULIET Study

Duration of Response	**Results**
Overall DOR for responders (months)	**N = 34**
Median DOR[a,b]	NE
(95% CI)	(5.1, NE)
Range[c]	(0.03+ – 11.3+)
Median Follow-up (95% CI)[b]	9.4 (7.9, 10.8)
DOR if BOR is CR	**N = 22**
Median DOR[a,b]	NE
(95% CI)	(10.0, NE)
Range[c]	(1.5+ – 11.3+)
DOR if BOR is PR	**N = 12**
Median DOR[a,b]	3.4
(95% CI)	(1.0, NE)
Range[c]	(0.03+ – 11.3+)

CR, Complete Response; DOR, Duration of Response: NE, not estimable, PR, partial response
[a]Among all responders. DOR measured from date of first objective response to date of progression or death from relapse.
[b]Kaplan-Meier estimate in months
[c]A + sign indicates a censored value

15 REFERENCES

1. Porter, D. et al (2015). Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia (Table S4A). Sci. Transl. Med., 303ra139. DOI: 10.1126/scitranslmed.aac5415

16 HOW SUPPLIED/STORAGE AND HANDLING

KYMRIAH is supplied as a frozen suspension of genetically modified autologous T cells in an infusion bag(s) labeled for the specific recipient. KYMRIAH is shipped directly to the cell lab associated with the infusion center in a liquid nitrogen Dewar. Product and patient-specific labels are located inside the Dewar.

Ped ALL: NDC 0078-0846-19

DLBCL: NDC 0078-0958-19

- Confirm patient identity upon receipt.
- Store infusion bag(s) in a temperature-monitored system less than or equal to minus 120°C, e.g., in the vapor phase of liquid nitrogen.
- Use closed, break-proof, leak-proof containers when transporting infusion bags within the facility.
- Thaw KYMRIAH prior to infusion *[see Dosage and Administration (2)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Ensure that patients understand the risk of manufacturing failure. This has been reported in up to 9% of manufacturing attempts. In case of a manufacturing failure, a second manufacturing of KYMRIAH may be attempted. In addition, while the patient awaits the product, additional chemotherapy (not the lymphodepletion) may be necessary and may increase the risk of adverse events during the pre-infusion period.

Prior to infusion, advise patients of the following risks:

- Cytokine Release Syndrome (CRS) -- Report signs and symptoms of CRS (high fever, difficulty breathing, chills/shaking chills, severe nausea, severe vomiting, severe diarrhea, severe muscle pain, severe joint pain, very low blood pressure, or dizziness/lightheadedness) to their healthcare professional *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*.
- Neurological Toxicities -- Report altered or decreased consciousness, delirium, confusion, agitation, seizures, difficulty speaking and understanding, or loss of balance to their healthcare professional *[see Warnings and Precautions (5.2), Adverse Reactions (6.1)]*.
- Serious Infections -- KYMRIAH may cause serious infections. Advise patients that they will be screened for HBV, HCV, and HIV before collection of cells *[see Warnings and Precautions (5.5), Adverse Reactions (6.1)]*.
- Hypogammaglobulinemia -- Patients may need to receive immunoglobulin replacement for an indefinite amount of time following treatment with KYMRIAH. Patients should tell their physician about their treatment with KYMRIAH before receiving a live virus vaccine *[see Warnings and Precautions (5.7), Adverse Reactions (6.1)]*.
- Driving and Engaging in Hazardous Occupations -- Patients should refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks after treatment *[see Warnings and Precautions (5.9)]*.
- Prolonged Cytopenia -- Patient may exhibit signs or symptoms associated with bone marrow suppression (i.e., neutropenia, thrombocytopenia and anemia) for several weeks following lymphodepleting chemotherapy and KYMRIAH.

Patients should be instructed to contact Novartis Pharmaceuticals Corporation at 1-844-4KYMRIAH if they get secondary malignancies *[see Warnings and Precautions (5.8)]*.

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T2020-153

MEDICATION GUIDE
KYMRIAH® (pronounced *KIM-RYE-AH)*
(tisagenlecleucel)

Read this Medication Guide before you start your KYMRIAH treatment. The more you know about your treatment, the more active you can be in your care. Talk with your healthcare provider if you have questions about your health condition or treatment. Reading this Medication Guide does not take the place of talking with your healthcare provider about your treatment.

What is the most important information I should know about KYMRIAH?

KYMRIAH may cause side effects that are severe or life-threatening. Call your healthcare provider or get emergency help right away if you get any of the following:

- difficulty breathing
- fever (100.4°F/38°C or higher)
- chills/shaking chills
- confusion
- severe nausea, vomiting, diarrhea
- severe muscle or joint pain
- very low blood pressure
- dizziness/lightheadedness

It is important that you tell your health care providers that you have received KYMRIAH. Your healthcare providers may give you other medicines to treat your side effects.

What is KYMRIAH?

KYMRIAH is made from your own white blood cells and is a prescription cancer treatment used in patients up to 25 years old who have acute lymphoblastic leukemia (ALL) that is either relapsing (went into remission, then came back) or refractory (did not go into remission after receiving other leukemia treatments). It is also used in patients with non-Hodgkin lymphoma that has relapsed or is refractory after having at least two other kinds of treatment.

How will I get KYMRIAH?

Since KYMRIAH is made from your own white blood cells, your healthcare provider has to take some of your blood. This is called "leukapheresis." It takes 3 to 6 hours and may need to be repeated. A tube (intravenous catheter) will be placed in your vein to collect your blood.

Your blood cells are frozen and sent to the manufacturing site to make KYMRIAH. It takes about 3-4 weeks from the time your cells are received at the manufacturing site and shipped back to your health care provider, but the time may vary.

Before you get KYMRIAH, your healthcare provider may give you chemotherapy for a few days to prepare your body.

When your body is ready, your healthcare provider will give you KYMRIAH through a tube (intravenous catheter) in your vein. This usually takes less than one hour.

You should plan to stay within 2 hours of the location where you received your treatment for at least 4 weeks after getting KYMRIAH. Your healthcare provider will check to see if your treatment is working and help you with any side effects that occur.

What should I avoid after receiving KYMRIAH?

- Do not drive, operate heavy machinery, or do other dangerous things for 8 weeks after you get KYMRIAH because the treatment can cause temporary memory and coordination problems, including sleepiness, confusion, weakness, dizziness, and seizures.
- Do not donate blood, organs, tissues and cells for transplantation.

What are the possible or reasonably likely side effects of KYMRIAH?

The most common side effects of KYMRIAH are:

- difficulty breathing
- fever (100.4°F/38°C or higher)
- chills/shaking chills
- confusion
- severe nausea, vomiting, diarrhea
- severe muscle or joint pain
- very low blood pressure
- dizziness/lightheadedness
- headache

KYMRIAH can increase the risk of life-threatening infections that may lead to death. Tell your healthcare provider right away if you develop fever, chills, or any signs or symptoms of an infection.

KYMRIAH can lower one or more types of your blood cells (red blood cells, white blood cells, or platelets). After treatment, your healthcare provider will test your blood to check for this. Tell your healthcare provider right away if you get a fever, are feeling tired, or have bruising or bleeding.

Having KYMRIAH in your blood may cause a false-positive HIV test result by some commercial tests.

These are not all the possible side effects of KYMRIAH. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of KYMRIAH.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

Do not use KYMRIAH for a condition for which it was not prescribed.

Talk to your healthcare provider about any concerns. You can ask your healthcare provider for information about KYMRIAH that is written for healthcare professionals.

For more information, go to KYMRIAH.com or call 1-844-NVS-CART (1-844-687-2278).

Manufactured and Distributed by: **Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936.**

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This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: December 2020

T2020-154