

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KYMRIA[®] safely and effectively. See full prescribing information for KYMRIA[®].

KYMRIA[®] (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 KYMRIA[®]. Do not administer KYMRIA[®] 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 KYMRIA[®], including concurrently with CRS. Monitor for neurological events after treatment with KYMRIA[®]. Provide supportive care as needed. (5.2)
- KYMRIA[®] is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIA[®] REMS. (5.3)

INDICATIONS AND USAGE

KYMRIA[®] 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: KYMRIA[®] 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 KYMRIA[®]. (2.3)
- Do NOT use a leukodepleting filter. (2.3)
- 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 KYMRIA[®] 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 10⁶ CAR-positive viable T cells per kg body weight intravenously. (2.1)
 - For patients above 50 kg, administer 0.1 to 2.5 x 10⁸ 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 10⁸ 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 KYMRIA[®] contains 0.2 to 5.0 x 10⁶ CAR-positive viable T cells per kg of body weight for patients 50 kg or less, or 0.1 to 2.5 x 10⁸ CAR-positive viable T cells for patients more than 50 kg, suspended in one to three patient-specific infusion bag(s) for IV infusion. (3)

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

A single dose of KYMRIA[®] contains 0.6 to 6.0 x 10⁸ CAR-positive viable T cells suspended in one to three patient-specific infusion bag(s) for IV 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 KYMRIA[®] 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 KYMRIA[®]. (5.7)
- Secondary Malignancies: In the event that a secondary malignancy occurs after treatment with KYMRIA[®], contact Novartis Pharmaceuticals Corporation at 1-844-4KYMRIA[®]. (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 KYMRIA[®]. (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, infections-pathogen unspecified, hypogammaglobulinemia, fever, decreased appetite, viral infectious disorders, headache, febrile neutropenia, bleeding episodes, vomiting, encephalopathy, diarrhea, hypotension, cough, nausea, bacterial infectious disorders, pain, hypoxia, fatigue, acute kidney injury, and arrhythmia. (6.1)

Adult Relapsed or Refractory Diffuse Large B-cell Lymphoma: The most common adverse reactions (incidence greater than 20%) are CRS, infections-pathogen unspecified, fever, diarrhea, nausea, fatigue, hypotension, edema, bleeding episodes, dyspnea, and headache. (6.1)

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: 8/2021

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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 KYMRIA. Do not administer KYMRIA 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 KYMRIA, including concurrently with CRS. Monitor for neurological events after treatment with KYMRIA. Provide supportive care as needed [see *Warnings and Precautions (5.2)*].
- KYMRIA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIA REMS [see *Warnings and Precautions (5.3)*].

1 INDICATIONS AND USAGE

KYMRIA 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: KYMRIA 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)

KYMRIA 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 10⁶ CAR-positive viable T cells per kg body weight
- Patients above 50 kg: administer 0.1 to 2.5 x 10⁸ CAR-positive viable T cells

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

KYMRIA 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 10⁸ CAR-positive viable T cells

2.3 Administration

Preparing Patient for KYMRIA Administration with Lymphodepletion

- Confirm availability of KYMRIA 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/m² intravenous daily for 4 days) and cyclophosphamide (500 mg/m² intravenous daily for 2 days starting with the first dose of fludarabine). Infuse KYMRIA 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/m² IV daily for 3 days) and cyclophosphamide (250 mg/m² IV daily for 3 days starting with the first dose of fludarabine).
- Alternate lymphodepleting chemotherapy: bendamustine 90 mg/m² IV 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 KYMRIA[®] 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 10⁹/L within 1 week prior to KYMRIA[®] infusion.

Preparation of KYMRIA[®] for Infusion and Administration

Delay the infusion of KYMRIA[®] 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)*].

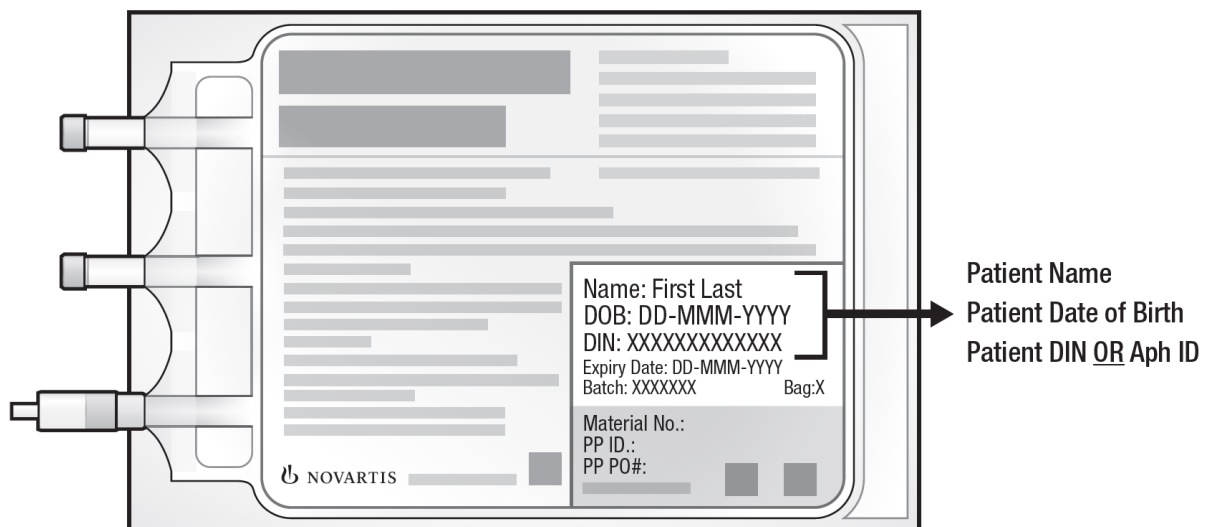
A KYMRIA[®] dose may be contained in one to three cryopreserved patient specific infusion bag(s). Verify the number of bags received for the dose of KYMRIA[®] with the Certificate of Conformance (CoC) and Certificate of Analysis (CoA). Coordinate the timing of thaw of KYMRIA[®] and infusion in the following manner. Confirm the infusion time in advance, and adjust the start time for thaw so that KYMRIA[®] 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 KYMRIA[®] 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 KYMRIA[®] infusion. Avoid prophylactic use of systemic corticosteroids, as it may interfere with the activity of KYMRIA[®].
3. Confirm patient identity: Prior to KYMRIA[®] preparation, match the patient's identity with the patient identifiers on each KYMRIA[®] infusion bag(s). KYMRIA[®] 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. KYMRIA[®] 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 sodium chloride 9 mg/mL (0.9%) solution for injection.
 - Infuse all contents of the infusion bag.
 - Rinse the infusion bag with 10 mL to 30 mL sodium chloride 9 mg/mL (0.9%) solution for injection 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
<i>Prodromal Syndrome:</i> Low-grade fever, fatigue, anorexia	Observe in person; exclude infection; administer antibiotics per local guidelines if neutropenic; provide symptomatic support.
<i>CRS requiring mild intervention (one or more of the following):</i> <ul style="list-style-type: none"> – High fever – Hypoxia – Mild hypotension 	Administer antipyretics, oxygen, intravenous fluids and/or low-dose vasopressors as needed.
<i>CRS requiring moderate to aggressive intervention (one or more of the following):</i> <ul style="list-style-type: none"> – 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 	<ul style="list-style-type: none"> • Administer high dose or multiple vasopressors, oxygen, mechanical ventilation and/or other supportive care as needed. • Administer tocilizumab <ul style="list-style-type: none"> - 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 KYMRIAHA contains 0.2 to 5.0 x 10⁶ CAR-positive viable T cells per kg of body weight for patients 50 kg and below or 0.1 to 2.5 x 10⁸ 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 KYMRIAHA contains 0.6 to 6.0 x 10⁸ 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 KYMRIAHA. CRS occurred in 61 (77%) of the 79 pediatric and young adult patients with r/r ALL and 85 (74%) of the 115 adult patients with r/r DLBCL receiving KYMRIAHA, including ≥ Grade 3 (Penn grading system¹) in 48% of patients with r/r ALL and in 23% of patients

with r/r DLBCL. The median times to onset and resolution of CRS for patients with r/r ALL were 3 days (range: 1-22; 1 patient with onset after Day 10) and 8 days (range: 1-36), respectively. The median times to onset and resolution of CRS for patients with r/r DLBCL were 3 days (range: 1-51; 1 patient with onset after Day 10) and 7 days (range: 2-30), respectively.

Of the 61 patients with r/r ALL who had CRS, 31 (51%) received tocilizumab. Ten (16%) patients received two doses of tocilizumab and 3 (5%) patients received three doses of tocilizumab; 17 (28%) patients received addition of corticosteroids (e.g., methylprednisolone). Of the 85 patients with r/r DLBCL who had CRS, 19 (22%) received systemic tocilizumab or corticosteroids. Seven (8%) patients received a single dose of tocilizumab and 11 (13%) patients received two doses of tocilizumab; 11 (13%) patients received corticosteroids in addition to tocilizumab. One patient 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 KYMRIA[®] 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 (93% in r/r ALL; 85% in r/r DLBCL), hypotension (69% in r/r ALL; 45% in r/r DLBCL), hypoxia (57% in r/r ALL; 35% in r/r DLBCL), and tachycardia (26% in r/r ALL; 13% in r/r DLBCL). CRS may be associated with hepatic, renal, and cardiac dysfunction, and coagulopathy.

Delay the infusion of KYMRIA[®] 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 at least two doses of tocilizumab are available on site prior to infusion of KYMRIA[®]. Monitor patients for signs or symptoms of CRS for at least 4 weeks after treatment with KYMRIA[®]. 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.

5.2 Neurological Toxicities

Neurological toxicities including severe or life-threatening reactions, occurred in 56 (71%) of the 79 patients with r/r ALL and 69 (60%) of the 115 patients with r/r DLBCL following treatment with KYMRIA[®], including \geq Grade 3 in 22% of patients with r/r ALL and 19% of patients with r/r DLBCL. Among patients who had a neurological toxicity, 83% occurred within 8 weeks following KYMRIA[®] infusion.

The median time to the first event was 6 days from infusion (range: 1-301) for patients with r/r ALL and 5 days (range: 1-368) for patients with r/r DLBCL. The median duration was 7 days for patients with r/r ALL and 17 days for patients with r/r DLBCL. Resolution occurred within 3 weeks in 71% of patients with r/r ALL and 50% 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 KYMRIA[®] include headache (35% in r/r ALL; 21% in r/r DLBCL), encephalopathy 30% in r/r ALL; 16% in r/r DLBCL), delirium (19% in r/r ALL; 5% in r/r DLBCL), anxiety (16% in r/r ALL; 10% in r/r DLBCL), sleep disorders (11% in r/r ALL; 10% in r/r DLBCL), dizziness (5% in r/r ALL; 12% in r/r DLBCL), tremor (8% in r/r ALL; 6% r/r DLBCL), and peripheral neuropathy (4% in r/r ALL; 12% in r/r DLBCL). Other manifestations included seizures and aphasia.

Monitor patients for neurological events and exclude other causes for neurological symptoms. Provide supportive care as needed for KYMRIA[®]-associated neurological events.

5.3 KYMRIA[®] REMS to Mitigate Cytokine Release Syndrome and Neurological Toxicities

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

- Healthcare facilities that dispense and administer KYMRIA[®] 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 KYMRIA[®] infusion, if needed for treatment of CRS.
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer KYMRIA[®] are trained about the management of CRS and neurological toxicities.

Further information is available at www.kymriah-rem.com or 1-844-4KYMRIA[®].

5.4 Hypersensitivity Reactions

Allergic reactions may occur with infusion of KYMRIA[®]. Serious hypersensitivity reactions, including anaphylaxis, may be due to the DMSO or dextran 40 in KYMRIA[®]. Observe patients for hypersensitivity reactions during the infusion.

5.5 Serious Infections

Infections, including life-threatening or fatal infections, occurred in 125 (64%) of 194 patients with r/r ALL or r/r DLBCL after KYMRIA[®] infusion. Seventy-seven patients (40%) 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 KYMRIA[®] infusion, infection prophylaxis should follow local guidelines. Patients with active uncontrolled infection should not start KYMRIA[®] treatment until the infection is resolved. Monitor patients for signs and symptoms of infection after treatment with KYMRIA[®] and treat appropriately [see *Dosage and Administration (2.3)*].

Febrile neutropenia (\geq Grade 3) was also observed in 34% of patients with r/r ALL and 17% of patients with r/r DLBCL after KYMRIA[®] 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.

There is no experience with manufacturing KYMRIA[®] for patients with a positive test for HIV or with active HBV or active HCV. 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 KYMRIA[®] infusion.

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

In the JULIET study (Study 2), \geq Grade 3 cytopenias not resolved by Day 28 following KYMRIA[®] treatment included thrombocytopenia (39%) and neutropenia (25%) among 115 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 KYMRIA[®] infusion or until CRS has resolved.

5.7 Hypogammaglobulinemia

Hypogammaglobulinemia and agammaglobulinemia related to B-cell aplasia can occur in patients after KYMRIA[®] infusion.

Hypogammaglobulinemia was reported in 53% of patients treated with KYMRIA[®] for r/r ALL and 17% of patients with r/r DLBCL [see *Clinical Pharmacology (12.3)*].

Monitor immunoglobulin levels after treatment with KYMRIA[®] and manage using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement standard guidelines.

Immunization with Live Vaccine

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.

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 79 pediatric and young adult patients with relapsed/refractory (r/r) B-cell ALL (ELIANA Study) and 115 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 79 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 (78%), infections-pathogen unspecified (57%), hypogammaglobulinemia (53%), fever (42%), decreased appetite (38%), viral infectious disorders (38%), headache (35%), febrile neutropenia (34%), bleeding episodes (32%), vomiting (32%), encephalopathy (30%), diarrhea (29%), hypotension (29%), cough (27%), nausea (27%), bacterial infectious disorders (27%), pain (25%), hypoxia (25%), fatigue (23%), acute kidney injury (22%), and arrhythmia (22%).

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 ($\geq 10\%$) Following Treatment with KYMRIAH in Pediatric and Young Adult r/r B-cell ALL (N = 79)

Adverse Reaction	All Grades (%)	Grades 3 or Higher (%)
<i>Blood and lymphatic system disorders</i>		
Febrile Neutropenia	34	34
Bleeding episodes ^a	32	10
<i>Cardiac disorders</i>		
Arrhythmia ^b	22	4
<i>Gastrointestinal disorders</i>		
Vomiting	32	1
Diarrhea	29	1
Nausea	27	3
Abdominal pain ^c	18	3
Constipation	18	0
<i>General disorders and administration site conditions</i>		
Fever	42	13
Pain ^d	25	3
Fatigue ^e	23	0
Edema ^f	19	1
<i>Immune system disorders</i>		
Cytokine release syndrome	77	48
Hypogammaglobulinemia ^g	53	13
<i>Infections and infestations</i>		
Infections-pathogen unspecified	57	27
Viral infectious disorders	38	22
Bacterial infectious disorders	27	16
Fungal infectious disorders	15	9
<i>Investigations</i>		
Serum ferritin increased	10	3
<i>Metabolism and nutrition disorders</i>		
Decreased appetite	38	15
Hypocalcemia	20	6
<i>Musculoskeletal and connective tissue disorders</i>		
Back pain	13	4
Myalgia	13	0
Arthralgia	10	1
<i>Nervous system disorders</i>		
Headache ^h	35	3
Encephalopathy ⁱ	30	9
<i>Psychiatric disorders</i>		
Delirium ^j	19	4
Anxiety	16	3
Sleep disorder ^k	11	0
<i>Renal and urinary disorders</i>		
Acute kidney injury ^l	22	14

Adverse Reaction	All Grades (%)	Grades 3 or Higher (%)
<i>Respiratory, thoracic and mediastinal disorders</i>		
Cough ^m	27	0
Hypoxia	25	20
Dyspnea ⁿ	18	13
Pulmonary edema	15	9
Nasal congestion	11	0
Oropharyngeal pain	10	0
Pleural effusion	10	4
Tachypnea	10	5
<i>Skin and subcutaneous tissue disorders</i>		
Rash ^o	18	1
<i>Vascular disorders</i>		
Hypotension	29	20
Hypertension	19	5

^aBleeding episodes includes anal hemorrhage, catheter site hemorrhage, cerebral hemorrhage, conjunctival hemorrhage, contusion, cystitis hemorrhagic, disseminated intravascular coagulation, epistaxis, gastrointestinal hemorrhage, gingival bleeding, hemarthrosis, hematemesis, hematuria, hemoptysis, melena, menorrhagia, mouth hemorrhage, peritoneal hematoma, petechiae, pharyngeal hemorrhage, purpura, retinal hemorrhage, vaginal hemorrhage.

^bArrhythmia includes tachycardia.

^cAbdominal pain includes abdominal pain, abdominal pain upper.

^dPain includes pain and pain in extremity.

^eFatigue includes fatigue and malaise.

^fEdema includes face edema, generalized edema, localized edema, edema peripheral.

^gHypogammaglobulinemia includes hypogammaglobulinemia, immunoglobulins decreased, blood immunoglobulin G decreased, blood immunoglobulin A decreased, blood immunoglobulin M decreased, immunodeficiency, immunodeficiency common variable.

^hHeadache includes headache and migraine.

ⁱEncephalopathy includes encephalopathy, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, lethargy, mental status changes, somnolence, memory impairment, and automatism.

^jDelirium includes delirium, agitation, hallucination, hallucination visual, irritability, restlessness.

^kSleep disorder includes sleep disorder, insomnia and nightmare.

^lAcute kidney injury includes acute kidney injury, anuria, azotemia, renal failure, renal tubular dysfunction, renal tubular necrosis, and blood creatinine increased.

^mCough includes cough and productive cough.

ⁿDyspnea includes dyspnea and respiratory distress, respiratory failure.

^oRash includes dermatitis, 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: coagulopathy (6%), hemophagocytic lymphohistiocytosis (6%), pancytopenia (3%),

Cardiac Disorders: cardiac failure^a (9%), cardiac arrest (4%)

Eye disorders: Visual impairment (3%)

Gastrointestinal disorders: abdominal distention (4%), ascites (4%), stomatitis (4%), abdominal compartment syndrome (1%), dry mouth (1%)

General disorders and administration site conditions: chills (9%), asthenia (4%), influenza-like illness (3%), multiple organ dysfunction syndrome (3%)

Immune system disorders: infusion related reaction (6%), graft versus host disease (3%)

Investigations: prothrombin time prolonged (4%), fibrin D dimer increased (3%), weight decreased (3%)

Metabolism and nutrition disorders: fluid overload (9%), tumor lysis syndrome (6%), hypercalcemia (4%)

Musculoskeletal and connective tissue disorders: musculoskeletal pain (6%)

Nervous System: tremor (8%), seizure^b (6%), dizziness (5%), peripheral neuropathy^c (4%), speech disorder^d (3%), motor dysfunction^e (1%), neuralgia (1%)

Respiratory, thoracic, and mediastinal disorders: acute respiratory distress syndrome (4%), lung infiltration (1%)

Skin and subcutaneous tissue disorders: pruritus (9%), erythema (6%), hyperhidrosis (4%), night sweats (1%)

Vascular disorders: capillary leak syndrome (3%), thrombosis (3%), flushing (1%)

^aCardiac failure includes cardiac failure, cardiac failure congestive, left ventricular dysfunction, right ventricular dysfunction.

^bSeizure includes generalized tonic-clonic seizure and seizure.

^cPeripheral neuropathy includes hyperesthesia, hypoesthesia, paresthesia.

^dSpeech disorder includes aphasia and dysarthria.

^eMotor dysfunction includes muscle spasms.

Laboratory Abnormalities

Table 3. Grade 3 or 4 Laboratory Abnormalities occurring in > 10% of Patients Following Treatment with KYMRIA[®] in Pediatric and Young Adult r/r B-cell ALL based on CTCAE (N = 79)

Laboratory Abnormality	Grade 3 or 4 (%)
Hematology	
Blood fibrinogen decreased	11
Biochemistry	
Aspartate aminotransferase increased	29
Hypokalemia	28
Alanine aminotransferase increased	22
Hypophosphatemia	20
Hyperbilirubinemia	19
Hyperglycemia	13

^aCTCAE = Common Terminology Criteria for Adverse Events version 4.03.

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

Table 4. Prolonged Cytopenias Following Treatment with KYMRIA[®] 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 \geq 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) 115 adults with r/r DLBCL received a single intravenous dose of KYMRIA[®] [see Clinical Studies (14.2)]. The most common adverse reactions (incidence > 20%) were cytokine release syndrome, infections-pathogen unspecified, fever, diarrhea, nausea, fatigue, hypotension, edema, bleeding episodes, dyspnea, and headache.

The study population characteristics were: median age of 56 years (range: 22 to 76 years), 80% DLBCL; a median of 3 prior lines of therapy (range: 1-6), 49% had a prior autologous hematopoietic stem cell transplantation, and 32% had received prior radiation therapy. One hundred seven patients (93%) received lymphodepleting chemotherapy prior to KYMRIA[®], that included fludarabine (n = 85) 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 $\geq 10\%$ Following Treatment with KYMRIA[®] in Adult r/r DLBCL (N = 115)

Adverse Reaction	All Grades (%)	Grades 3 or Higher (%)
<i>Blood and lymphatic system disorders</i>		
Bleeding episodes ^a	22	8
Febrile Neutropenia	17	17
<i>Cardiac disorders</i>		
Arrhythmia ^b	17	5
<i>Gastrointestinal disorders</i>		
Diarrhea	31	1
Nausea	29	1
Constipation	17	1
Abdominal pain ^c	10	2
<i>General disorders and administration site conditions</i>		
Fever	35	5
Fatigue ^d	27	6
Edema ^e	23	2
Pain ^f	14	3
Chills	12	0
<i>Immune system disorders</i>		
Cytokine release syndrome	74	23
Hypogammaglobulinemia ^g	17	6
<i>Infections and infestations</i>		
Infections-pathogen unspecified	48	26
Bacterial infectious disorders	15	8
Fungal infectious disorders	11	5
Viral infectious disorders	11	2
<i>Investigations</i>		
Weight decreased	12	3
<i>Metabolism and nutrition disorders</i>		
Decreased appetite	14	3
<i>Musculoskeletal and connective tissue disorders</i>		
Arthralgia	10	0
<i>Nervous system disorders</i>		
Headache ^h	21	1
Encephalopathy ⁱ	16	11
Peripheral neuropathy ^j	12	3
Dizziness ^k	12	2
<i>Psychiatric disorders</i>		
Anxiety	10	1
Sleep disorder ^l	10	0
<i>Renal and Urinary Disorders</i>		
Acute kidney injury ^m	17	6
<i>Respiratory, thoracic and mediastinal disorders</i>		

Adverse Reaction	All Grades (%)	Grades 3 or Higher (%)
Dyspnea ⁿ	21	6
Cough ^o	17	0
<i>Skin and subcutaneous tissue disorders</i>		
Rash ^p	11	0
<i>Vascular disorders</i>		
Hypotension ^q	25	9

^aBleeding episodes includes anal hemorrhage, blood urine present, cerebral hemorrhage, contusion, cystitis hemorrhagic, disseminated intravascular coagulation, duodenal ulcer hemorrhage, epistaxis, eye contusion, gastrointestinal hemorrhage, hematemesis, hematochezia, hematuria, large intestinal hemorrhage, melena, mouth hemorrhage, petechiae, pharyngeal hemorrhage, post procedural hemorrhage, pulmonary hemorrhage, purpura, retinal hemorrhage, traumatic hematoma, tumor hemorrhage, upper gastrointestinal hemorrhage.

^bArrhythmia includes atrial fibrillation, supraventricular tachycardia, tachycardia, and ventricular extrasystoles.

^cAbdominal pain includes abdominal discomfort, abdominal pain, and abdominal pain upper.

^dFatigue includes fatigue and malaise.

^eEdema includes face edema, generalized edema, localized edema, edema peripheral, peripheral swelling.

^fPain includes pain and pain in extremity.

^gHypogammaglobulinemia includes blood immunoglobulin G decreased, immunodeficiency, immunoglobulins decreased and hypogammaglobulinemia.

^hHeadache includes headache and migraine.

ⁱEncephalopathy includes encephalopathy, cognitive disorder, confusional state, disturbance in attention, lethargy, mental status changes, somnolence, memory impairment, metabolic encephalopathy and thinking abnormal.

^jPeripheral neuropathy includes paraesthesia, hypoaesthesia, hyperaesthesia, peripheral sensory neuropathy, neuropathy peripheral, cranial nerve paralysis, demyelinating polyneuropathy, Horner's syndrome, polyneuropathy, and sciatica.

^kDizziness includes dizziness, presyncope, and syncope.

^lSleep disorder includes insomnia and sleep disorder.

^mAcute kidney injury includes acute kidney injury, blood creatinine abnormal, and blood creatinine increased.

ⁿDyspnea includes dyspnea, dyspnea exertional, respiratory distress, and respiratory failure.

^oCough includes cough, productive cough, and upper-airway cough syndrome.

^pRash includes dermatitis, dermatitis acneiform, dermatitis contact, rash, rash maculo-papular, rash papular, and rash pruritic.

^qHypotension 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: pancytopenia (3%), hemophagocytic lymphohistiocytosis (2%), B-cell aplasia (1%)

Cardiac Disorders: cardiac arrest (3%), cardiac failure^a (1%)

Eye disorders: visual impairment^b (6%)

Gastrointestinal disorders: vomiting (9%), stomatitis (6%), dry mouth (5%), abdominal distension (3%), ascites (3%)

General disorders and administration site conditions: influenza-like illness (9%), asthenia (7%), multiple organ dysfunction syndrome (3%)

Immune system disorders: infusion related reaction (3%)

Investigations: fibrin D dimer increased (4%), serum ferritin increased (4%)

Metabolism and nutrition disorders: hypocalcemia (5%), hypercalcemia (4%), fluid overload (3%), tumor lysis syndrome (2%)

Musculoskeletal and connective tissue disorders: back pain (5%), myalgia (5%), musculoskeletal pain (4%)

Nervous System: motor dysfunction^c (6%), tremor^d (6%), speech disorder^e (4%), neuralgia^f (3%), seizure^g (3%), ataxia^h (2%), ischemic cerebral infarction (1%)

Psychiatric disorders: deliriumⁱ (5%)

Respiratory, thoracic, and mediastinal disorders: hypoxia (8%), oropharyngeal pain^j (8%), pleural effusion (5%), nasal congestion (4%), pulmonary edema^k (3%), tachypnea (3%)

Skin and subcutaneous tissue disorders: night sweats (5%), pruritus (4%), hyperhidrosis (3%), erythema (2%)

Vascular disorders: thrombosis^l (6%), hypertension (4%), capillary leak syndrome (1%)

^aCardiac failure includes cardiac failure congestive.

^bVisual impairment includes vision blurred and visual impairment.

^cMotor dysfunction includes muscle spasms, muscle twitching, myoclonus and myopathy.

^dTremor includes dyskinesia and tremor.

^eSpeech disorder includes speech disorder, aphasia, and dysarthria.

^fNeuralgia includes neuralgia and sciatica.

^gSeizure includes PTs seizure and status epilepticus.

^hAtaxia includes ataxia and dysmetria.

ⁱDelirium includes delirium, agitation, and irritability.

^jOropharyngeal pain includes oral pain and oropharyngeal pain.

^kPulmonary edema includes acute pulmonary edema and pulmonary edema.

^lThrombosis includes deep vein thrombosis, embolism, pulmonary embolism, thrombosis, vena cava thrombosis, and venous thrombosis.

Laboratory Abnormalities

Table 6. Grade 3 or 4 Laboratory Abnormalities occurring in > 10% of Patients Following KYMRIA[®] Infusion in Adult r/r DLBCL Patients Based on CTCAE^a N = 115

Laboratory Parameter	Grade 3 or 4 (%)
Hematology	
Lymphopenia	95
Neutropenia	82
Leukopenia	78
Anemia	59
Thrombocytopenia	56
Biochemistry	
Hypophosphatemia	24
Hypokalemia	13

^aCTCAE = Common Terminology Criteria for Adverse Events version 4.03.

6.2 Postmarketing Experience

The following adverse reaction has been identified during postapproval use of KYMRIA[®]. Because this reaction is reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate its frequency or establish a causal relationship to drug exposure.

- Anaphylactic reaction

6.3 Immunogenicity

In clinical studies, humoral immunogenicity of KYMRIA[®] was measured by determination of anti-murine CAR19 antibodies (anti-mCAR19) in serum pre- and post-administration. The majority of patients, 91% in ELIANA (Study 1) and 94% in JULIET (Study 2) tested positive for pre-dose anti-mCAR19 antibodies prior to KYMRIA[®] infusion. Treatment induced anti-mCAR19 antibodies were detected in 9% 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 KYMRIA[®]. Persistence of KYMRIA[®] 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 KYMRIA[®].

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

7 DRUG INTERACTIONS

HIV and the lentivirus used to make KYMRIA[®] 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 KYMRIA[®].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with KYMRIA[®] use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with KYMRIA[®] to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if KYMRIA[®] 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, KYMRIA[®] is not recommended for women who are pregnant, and pregnancy after KYMRIA[®] 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 KYMRIA[®] in human milk, the effect on the breastfed infant, and the effects on milk production. A risk to the breastfed infant cannot be excluded. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KYMRIA[®] and any potential adverse effects on the breastfed infant from KYMRIA[®] 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 KYMRIA[®].

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 KYMRIA[®].

Infertility

There are no data on the effect of KYMRIA[®] on male and female fertility.

8.4 Pediatric Use

The safety and efficacy of KYMRIA[®] have been established in pediatric patients with r/r B-cell ALL. Use of KYMRIA[®] is supported by a single-arm trial [*see Clinical Studies (14.1)*] that included 61 pediatric patients with r/r B-cell precursor ALL in the following age groups: 40 children (ages 2 years to less than 12 years) and 21 adolescents (ages 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 KYMRIA[®] in pediatric patients with relapsed or refractory DLBCL have not been established.

8.5 Geriatric Use

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

11 DESCRIPTION

KYMRIA[®] (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 2.5×10^8 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 5.0×10^6 CAR-positive viable T cells per kg body weight
- For patients above 50 kg: 0.1 to 2.5×10^8 CAR-positive viable T cells

Adult r/r DLBCL: A single dose of KYMRIAH may contain 0.6 to 6.0×10^8 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.

12.2 Pharmacodynamics

Due to the on-target effect of KYMRIAH, a period of B-cell aplasia is expected.

Among evaluable pediatric and young adult r/r B-cell ALL patients with an ongoing response at Month 24, 33% had no detectable B cells at baseline prior to infusion. At Month 24, 88% had no detectable B cells.

Most adult r/r DLBCL patients had B-cell depletion at baseline prior to infusion due to previous treatment with rituximab. Recovery of B-cell levels were observed with longer follow-up in some of the responding DLBCL patients after KYMRIAH infusion. Among evaluable adult r/r DLBCL patients with an ongoing response at Month 24, all patients had no detectable B cells at baseline prior to infusion or at Month 24.

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 KYMRIA[®] in Pediatric and Young Adult r/r B-cell ALL and Adult r/r DLBCL

Parameter	Summary Statistics	Pediatric ALL Responding Patients N = 62	Pediatric ALL Non-Responding Patients N = 8	r/r DLBCL Responding Patients (CR and PR) N = 34	r/r DLBCL Non-Responding Patients (SD/PD/Unknown) 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 _{0-28d} (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

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

The C_{max} and AUC_{0-28d} were similar between CR/CRi patients compared with non-responding (NR) patients.

KYMRIA[®] was present in the blood as well as bone marrow and was measurable beyond 2 years. Blood to bone marrow partitioning suggested that KYMRIA[®] distribution in bone marrow was 44% of that present in blood at Day 28 while at Months 3 and 6 KYMRIA[®] distributed at 67% and 69%, respectively, indicating high distribution to bone marrow.

Children < 10 years and between 10-18 years of age had similar- to 1.7-fold higher C_{max} and AUC_{0-28d} than adults. Due to small sample size and high variability, it is difficult to assess the impact of age on the pharmacokinetics of KYMRIA[®].

Description of Pharmacokinetics in Adult r/r DLBCL

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

KYMRIA[®] 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 used for CRS Management

Some patients required tocilizumab and corticosteroids for the management of CRS. KYMRIA[®] continues to expand and persist following treatment as per the CRS management algorithm (see Table 1). 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 = 28) treated with tocilizumab had 298% and 183% higher KYMRIA[®] AUC_{0-28d} and C_{max}, respectively, as compared to patients (N = 46) who did not receive tocilizumab. In addition, patients who received corticosteroids for CRS management (N=17) had 280% higher AUC_{0-28d} compared with patients who did not receive corticosteroids (N = 31).

Adult r/r DLBCL patients treated with tocilizumab (N = 18) had 238% (n = 14) and 311% (n = 16) higher KYMRIA[®] AUC_{0-28d} and C_{max}, respectively, as compared to patients (N = 97) who did not receive tocilizumab. In addition, patients who received corticosteroids for CRS management (N = 12) had 104% and 179% higher AUC_{0-28d} and C_{max}, respectively, as compared with patients who did not receive corticosteroids (N = 79).

Hepatic and renal impairment studies of KYMRIA[®] 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 KYMRIA[®]. *In vitro* expansion studies with transduced T cells (KYMRIA[®]) 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 KYMRIA 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 KYMRIA on fertility have been conducted.

14 CLINICAL STUDIES

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

The efficacy of KYMRIA 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/m² daily for 4 days and cyclophosphamide 500 mg/m² daily for 2 days) followed by a single dose of KYMRIA. Of the 22 patients who had a WBC count < 1000/μL, 20 received lymphodepleting chemotherapy prior to KYMRIA while 2 received KYMRIA infusion without lymphodepleting chemotherapy. Fifty-three patients received bridging chemotherapy between time of enrollment and lymphodepleting chemotherapy.

The efficacy of KYMRIA 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) (95% CI)	Not reached (7.5, NE ⁸)

¹CR/CRi was calculated based on all patients who received KYMRIA 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.

²The null hypothesis of CR/CRi less than or equal to 20% was rejected.

³CR (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.

⁴CRi (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.

⁵MRD (minimal residual disease) negative was defined as MRD by flow cytometry less than 0.01%.

⁶The null hypothesis of MRD-negative remission rate less than or equal to 15% was rejected.

⁷DOR (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).

⁸Not Estimable.

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

The efficacy and safety of KYMRIA[®] 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 allogeneic 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 $300/\mu\text{L}$.

Following 2 to 11 days after completion of lymphodepleting (LD) chemotherapy consisting of either fludarabine ($25 \text{ mg}/\text{m}^2$ i.v. daily for 3 days) and cyclophosphamide ($250 \text{ mg}/\text{m}^2$ i.v. daily for 3 days starting with the first dose of fludarabine) or bendamustine ($90 \text{ mg}/\text{m}^2$ i.v. daily for 2 days), KYMRIA[®] 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 $< 1000 \text{ cells}/\mu\text{L}$. 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 KYMRIA[®], 90% received physician's choice of bridging chemotherapy in the interval between start of screening and KYMRIA[®] 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 KYMRIA[®] infusion. Of the 24 patients not included, 8 had no evidence of disease at baseline prior to KYMRIA[®] 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 KYMRIA[®] 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 KYMRIA[®] 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 KYMRIA[®] (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 10). 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 KYMRIA[®] 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

^aAmong all responders. DOR measured from date of first objective response to date of progression or death from relapse.

^bKaplan-Meier estimate in months

^cA + 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 -- KYMRIA[®]H 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 KYMRIA[®]H. Patients should tell their physician about their treatment with KYMRIA[®]H before receiving a live 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 KYMRIA[®]H.

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

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T2021-116

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 healthcare 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 healthcare provider, but the time may vary.

While waiting for KYMRIAH to be made, your healthcare provider may give you therapy to stabilize your cancer.

In addition, 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 KYMRIA?

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

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

The most common side effects of KYMRIA 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

KYMRIA 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.

KYMRIA 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, weak, or short of breath, or have bruising or bleeding.

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

These are not all the possible side effects of KYMRIA. 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 KYMRIA.

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

Do not use KYMRIA 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 KYMRIA that is written for healthcare professionals.

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

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