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. (2.2, 2.3, 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)

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

For autologous use only.
For intravenous use only.

- Verify the patient's identity prior to infusion. (2.2)
- Premedicate with acetaminophen and an H1-antihistamine. (2.2)
- Confirm availability of tocilizumab prior to infusion. (2.2, 5.1)
- Dosing is based on the number of chimeric antigen receptor (CAR) positive viable T cells.
- 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)

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

A single-dose unit 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 a patient-specific infusion bag. See the Certificate of Analysis (CoA) for actual cell count. (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 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----------

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, and delirium. (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: 8/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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 *[see Dosage and Administration (2.2, 2.3), 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 patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

2 DOSAGE AND ADMINISTRATION

For autologous use only.

For intravenous use only.

2.1 Dose

- One treatment course consists of fludarabine and cyclophosphamide lymphodepleting chemotherapy followed by infusion of KYMRIAH *[see Clinical Studies (14)]*.
- KYMRIAH is provided in a single-dose unit containing chimeric antigen receptor (CAR)-positive viable T cells* based on the patient weight reported at the time of leukapheresis. The dose is:
  - For patients 50 kg or less: administer 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg body weight
  - For patients above 50 kg: administer 0.1 to 2.5 x 10^8 CAR-positive viable T cells

*See the Certificate of Analysis for the actual number of chimeric antigen receptor (CAR)-positive T cells in the product.

- 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.

2.2 Prepare 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)]*.

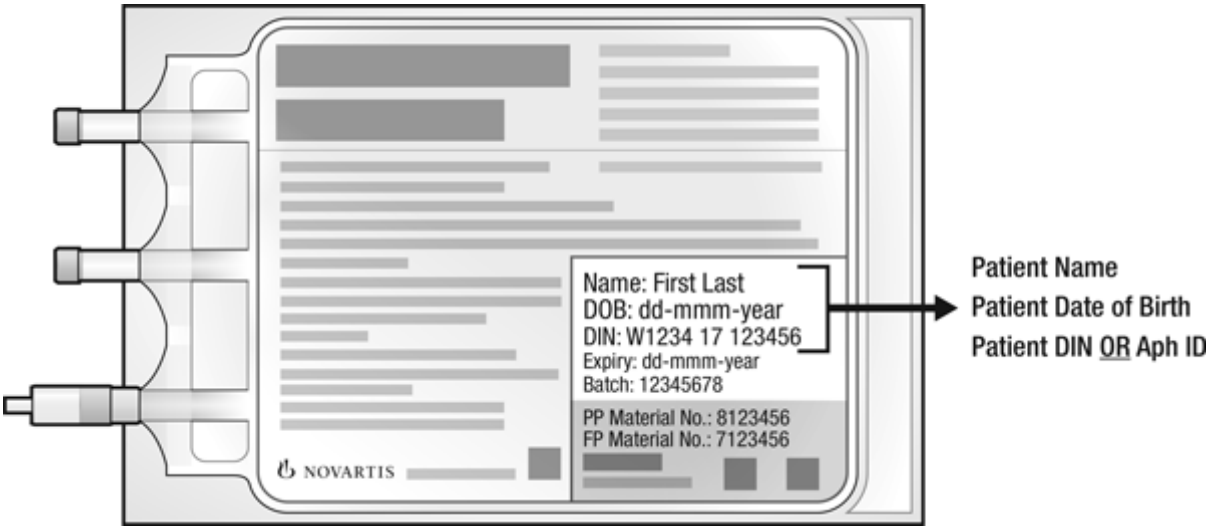
Coordinate the timing of thaw of KYMRIAH and infusion. Once thawed, KYMRIAH may be stored at room temperature (20°C to 25°C) for up to 30 minutes. Confirm the infusion time in advance, and adjust the start time for thaw so that KYMRIAH is available for infusion when the recipient is ready.

Preparation 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. Do not use corticosteroids at any time except in the case of a life-threatening emergency.

3. Confirm patient identity: Prior to KYMRIAH preparation, match the patient's identity with the patient identifiers on the KYMRIAH infusion bag. KYMRIAH is for autologous use only.

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



4. Inspect the infusion bag for any breaks or cracks prior to thawing. If the 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 KYMRIAH 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 KYMRIAH 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.
   - 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.

KYMRIAH contains human cells genetically modified with a lentivirus. Follow local biosafety guidelines applicable for handling and disposal of such products. The product is prepared from autologous blood collected by leukapheresis. KYMRIAH may carry a risk of transmitting infectious viruses to healthcare professionals handling the product. Accordingly, healthcare professionals should employ universal precautions to avoid potential transmission of infectious diseases when handling the product.

2.3 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.
***Overt CRS (one or more of the following)*:** – High fever – Hypoxia – Mild hypotension	Administer antipyretics, oxygen, intravenous fluids and/or low-dose vasopressors as needed.
***Severe or Life-Threatening CRS (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)
***Resistant CRS*:** No clinical improvement in 12 to 18 hours, or worsening at any time, despite prior management.	Administer multiple vasopressors, oxygen, mechanical ventilation and/or other supportive care as needed. 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 quickly. If no response to steroids within 24 hours, repeat the administration of tocilizumab at - 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) If no response to the second dose of tocilizumab within 24 hours, consider a third dose of tocilizumab or pursue alternative measures for treatment of CRS.

3 DOSAGE FORMS AND STRENGTHS

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 a single patient-specific infusion bag *[see How Supplied/Storage and Handling (16)]*. See the Certificate of Analysis (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

Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred following treatment with KYMRIAH. In Study 1, CRS occurred in 79% (54/68) of patients receiving KYMRIAH, including Grade 3 or 4 (Penn grading system[1]) CRS in 49% (33/68) of patients. The median time to onset of CRS was 3 days (range: 1-22 days). Of the 54 patients with CRS, 27 (50%) received tocilizumab; 7 (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). The median time to resolution of CRS was 8 days (range: 1-36 days).

Key manifestations of CRS include high fever, lower than normal blood pressure, difficulty breathing, and may be associated with hepatic, renal, and cardiac dysfunction, and coagulopathy.

Risk factors for severe CRS 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.

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 (2.2)]*.

Ensure that tocilizumab is 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)]*.

5.2 Neurological Toxicities

Neurological toxicities, which may be severe or life-threatening can occur following treatment with KYMRIAH. The majority of neurological toxicities occurred within 8 weeks following KYMRIAH infusion. In Study 1, neurological toxicities within 8 weeks after KYMRIAH infusion occurred in 65% of patients, including Grade 3 or 4 neurological toxicities in 18% of patients, and 75% of events resolved within 12 days. The most common neurological toxicities were headache (37%), encephalopathy (34%), delirium (21%), anxiety (13%), and tremor (9%). Other manifestations of neurological toxicities included disturbances in consciousness, disorientation, confusion, agitation, seizures, mutism and aphasia. Onset of neurological toxicity can be concurrent with CRS, following resolution of CRS or in the absence of CRS.

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

Serious infections, including life-threatening or fatal infections, occurred in patients after KYMRIAH infusion. In Study 1, infections (all Grades) after KYMRIAH infusion occurred in 40 patients (59%), including 24 patients (35%) with Grade 3-4 infections and 2 patients (3%) with fatal infections. Infections with an unknown pathogen occurred in 41% of patients, viral infections in 26%, bacterial infections in 19%, and fungal infections in 13%. Prior to KYMRIAH infusion, infection prophylaxis should follow local guidelines. 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 or 4) was also observed in 37% of patients 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. Hepatitis cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive, and also in patients who are HBsAg-negative but hepatitis B core antibody (anti-HBc) positive. HBV reactivation has occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg-negative, anti-HBc-positive and hepatitis B surface antibody [anti-HBs] positive).

HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg-negative and anti-HBc-positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases, increase in bilirubin levels, liver failure, and death can occur.

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 Grade 3 and 4 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 and 4 neutropenia or thrombocytopenia respectively. 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) can occur in patients with a complete remission (CR) after KYMRIAH infusion. In Study 1, 43% of patients had hypogammaglobulinemia. B-cell aplasia is an on-target effect of KYMRIAH and therefore a patient may experience hypogammaglobulinemia for as long as KYMRIAH persists *[see Clinical Pharmacology (12.3)]*.

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

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 2 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 leukemia. 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

Most common adverse reactions (incidence greater than 20%) are hypogammaglobulinemia, infections-pathogen unspecified, pyrexia, decreased appetite, headache, encephalopathy, bleeding, hypotension, tachycardia, nausea, diarrhea, vomiting, viral infectious disorders, hypoxia, fatigue, acute kidney injury, and delirium.

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 this section reflect exposure to KYMRIAH in the clinical trial (Study 1) in which 68 patients with pediatric and young adult relapsed/ refractory (R/R) B-cell ALL received CAR-positive viable T cells.

Based on a recommended dose which was weight-based, all patients received a single intravenous dose of KYMRIAH *[see Clinical Studies (14)]*. The most common adverse reactions 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 (22%), acute kidney injury (22%), and delirium (21%).

Eleven deaths were reported for patients who received KYMRIAH, of which 2 deaths occurred within 30 days of infusion. Seven were disease-related, three were attributed to infections, and one to intracerebral hemorrhage. Of the two deaths before Day 30, one patient died with CRS and progressive leukemia and the second patient had resolving CRS with abdominal compartment syndrome, coagulopathy, and renal failure when an intracranial hemorrhage occurred.

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

Table 2. Selected Adverse Reactions (≥ 10%) Following Treatment with KYMRIAH (N=68)

Adverse Reaction	**All Grades** (%)	**Grades 3 or Higher** (%)
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
Fatigue	22	0
Face edema	10	1
Edema peripheral	10	1
Chills	10	0
Immune system disorders		
Cytokine release syndrome	79	49
[c]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		
Pain in extremity	16	1
Myalgia	15	0
Arthralgia	12	1
Back pain	10	3
Nervous system disorders		
[d]Headache	37	3
[e]Encephalopathy	34	10
Psychiatric disorders		
[f]Delirium	21	4
Anxiety	13	3
Renal and urinary disorders		
[g]Acute kidney injury	22	13
Respiratory, thoracic and mediastinal disorders		
Hypoxia	24	18
Cough	19	0
Pulmonary edema	16	10
Tachypnea	12	6
Pleural effusion	10	4
Nasal congestion	10	0
Vascular disorders		
Hypotension	31	22
Hypertension	19	6

[a]Tachycardia includes tachycardia and sinus tachycardia.
[b]Abdominal pain includes abdominal pain, abdominal pain upper, gastrointestinal pain, abdominal pain lower.
[c]Hypogammaglobulinemia includes hypogammaglobulinemia, immunoglobulins decreased, blood immunoglobulin G decreased, blood immunoglobulin A decreased, blood immunoglobulin M decreased, hypogammaglobulinemia.
[d]Headache includes headache and migraine.
[e]Encephalopathy includes encephalopathy, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, lethargy, mental status changes, posterior reversible encephalopathy syndrome, somnolence, and automatism.
[f]Delirium includes delirium, agitation, hallucination, hallucination visual, irritability, restlessness.
[g]Acute kidney injury includes acute kidney injury, anuria, azotemia, renal failure, renal tubular dysfunction, renal tubular necrosis.

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: blood creatinine increased (7%), activated partial thromboplastin time prolonged (6%)

Nervous System: intracranial hemorrhage (1%), seizure (3%)

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

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

Vascular disorders: capillary leak syndrome (3%)

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 from Baseline Grade 0-2 to Grade 3-4 Following Treatment with KYMRIAH based on CTCAE[a] (N=68)

	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 and Grade 4 prolonged thrombocytopenia and prolonged neutropenia in responding patients.

Table 4. Prolonged Cytopenias Following Treatment with KYMRIAH

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

[a]Grade 3 and 4 observed within 14 days after Day 28 or Day 56 in responding patients

6.2 Immunogenicity

In clinical studies, humoral immunogenicity of KYMRIAH was measured by determination of anti-murine CAR19 antibodies (anti-m CAR19) in serum pre- and post-administration. The majority of patients (86%) tested positive for pre-dose anti-m CAR19 antibodies in Study 1; 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-m CAR19 antibodies compared with patients with negative post-infusion anti-m CAR19 antibodies. There is no evidence that the presence of preexisting and treatment-induced anti-mCAR19 antibodies impact the safety or effectiveness of KYMRIAH.

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 (NAT) 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. Use of KYMRIAH is supported by a single-arm trial *[see Clinical Studies (14)]* that included 52 pediatric patients with relapsed or refractory 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.

8.5 Geriatric Use

The safety and effectiveness of KYMRIAH have not been established in geriatric patients. Clinical studies of KYMRIAH for this indication did not include patients age 65 years and over.

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. The product is thawed prior to administration *[see Dosage and Administration (2.5), 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).

A single dose of KYMRIAH may contain up to 2.5 x 10^8 CAR-positive viable T cells provided in a patient-specific infusion bag. 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

The actual number of CAR-positive T cells in the product is reported on the Certificate of Analysis 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

Following infusion of KYMRIAH in pediatric and young adult relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) patients, KYMRIAH exhibited an initial rapid expansion followed by a bi-exponential decline. KYMRIAH should be administered within 30 minutes of thawing at approximately 10-20 mL per minute.

A summary of pharmacokinetic parameters of KYMRIAH is provided in Table 5 below.

Table 5. Pharmacokinetic Parameters of KYMRIAH

Parameter	Summary Statistics	Responding Patients N=62	Non-Responding Patients N=8
C_{max} (copies/mcg)	Geometric mean (CV%), n	34,700 (155.4), 61	20,000 (71.6%), 7
T_{max}‡ (day)	Median [min;max], n	9.91 [0.008;27], 61	20.0 [0.03;62.7], 7
AUC0-28d (copies/mcg*day)	Geometric mean (CV%), n	318,000 (177.8), 61	156,000 (99.4), 6
$T_{½}$ (day)	Geometric mean (CV%), n	16.8 (155.9), 54	2.52 (171.9), 3

‡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.

The C_{max} and AUC0-28d 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 AUC0-28d than adults. Due to small sample size and high variability, it is difficult to assess the impact of age on the pharmacokinetics of KYMRIAH.

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 are associated with higher CRS Grades *[see Warnings and Precautions (5.1)]*. Patients (n=18) treated with tocilizumab had 265% and 183% higher KYMRIAH AUC0-28d and C_{max}, respectively, as compared to patients (n=44) who did not receive

tocilizumab. Similarly, patients who received corticosteroids had 89% higher AUC0-28d compared with patients who did not receive corticosteroids.

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

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 (Study 1). In total, 107 patients were screened, 88 were enrolled, 68 were treated, and 63 were evaluable for efficacy. Nine percent of the enrolled subjects 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 6). 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 6 shows the efficacy results from this study.

Table 6. Efficacy Results in Pediatric and Young Adult Patients with R/R B-cell Precursor ALL

Results	**N=63**
CR/CRi[1,2]	52 (83%)
95% CI	(71%, 91%)
	p<0.0001
CR[3]	40 (63%)
CRi[4]	12 (19%)
CR or CRi with MRD-negative bone marrow[5,6]	52 (83%)
95% CI	(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.

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 one infusion bag 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. NDC 0078-0846-19

- Confirm patient identity upon receipt.
- Store infusion bag in the vapor phase of liquid nitrogen (less than or equal to minus 120°C) in a temperature-monitored system.
- 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)]*.

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

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

T2017-78

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 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). KYMRIAH is made from your own white blood cells.

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 to make KYMRIAH, 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

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**

T2017-79