DRUG DETERMINATION POLICY

Title: DDP-38 CAR-T Cell Immunotherapy

Effective Date: 12/15/2020

Physicians Health Plan
PHP Insurance Company
PHP Service Company

Important Information - Please Read Before Using This Policy

The following policy applies to health benefit plans administered by PHP and may not be covered by all PHP plans. Please refer to the member's benefit document for specific coverage information. If there is a difference between this general information and the member's benefit document, the member's benefit document will be used to determine coverage. For example, a member's benefit document may contain a specific exclusion related to a topic addressed in a coverage policy.

Benefit determinations for individual requests require consideration of:

1. The terms of the applicable benefit document in effect on the date of service.
2. Any applicable laws and regulations.
3. Any relevant collateral source materials including coverage policies.
4. The specific facts of the particular situation.

Contact PHP Customer Service to discuss plan benefits more specifically.

1.0 Policy:

This policy describes the determination process for coverage of specific drugs.

This policy does not guarantee or approve benefits. Coverage depends on the specific benefit plan. Drug Determination Policies are not recommendations for treatment and should not be used as treatment guidelines.

2.0 Background or Purpose:

CAR-T cell immunotherapy is covered through the medical benefit based on approval by the Health Plan. These criteria were developed and implemented to ensure appropriate use for the intended diagnoses and mitigation of toxicity, if possible.

3.0 Clinical Determination Guidelines:

Document the following with chart notes:

I. Kymriah intravenous (tisagenlecleucel IV).

A. Acute Lymphoblastic Leukemia (ALL) [must meet all listed below]:

1. Age: three to 25 years.

2. Prescriber/site: oncologist; Certified Healthcare Facility enrolled in the Kymriah REMS; training has been given to providers on the management of cytokine release syndrome (CRS) and neurological toxicities.

3. Diagnosis and severity [must meet all listed below]:

a. B-cell Precursor Acute Lymphoblastic Leukemia (ALL).

b. CD19 tumor expression.

c. Refractory to therapy or member has had at least two bone marrow relapses.

4. Other therapies: contraindicated, inadequate response or significant adverse effects to one of the therapies below:

    a. Stem Cell Transplant (SCT).

    b. Standard chemotherapy: two lines without complete response.

    c. Philadelphia chromosome positive: two prior lines of tyrosine kinase inhibitor (TKI) therapy (e.g. imatinib, dasatinib, ponatinib).

5. Dosage regimen: Kymriah intravenous (tisagenlecleucel IV).

    a. Infuse two to 14 days after completion of lymphodepleting chemotherapy (cyclophosphamide and fludarabine).

    b. Dose: less than 50 kg: 0.2 -5 x 10^6 CAR+ T cells per kg.; greater than 50 kg: 0.1-2.5 10^8 CAR+ T cells per kg.

B. Relapsed or Refractory Diffuse Large B-cell Lymphoma (DLBCL) [must meet all listed below]:

1. Age: at least 18 years.

2. Prescriber/site: oncologist; Certified Healthcare Facility enrolled in the Kymriah REMS; training has been given to providers on the management of cytokine release syndrome (CRS) and neurological toxicities.

3. Diagnosis and severity [must meet one listed below]:

    a. High-grade B-cell Lymphoma.

    b. DLBDL arising from follicular lymphoma.

    c. DLBL not otherwise specified.

4. Other therapies: contraindicated, inadequate response or significant adverse effects to one of the therapies below:

    a. Stem Cell Transplant (SCT).

    b. Standard chemotherapy: two lines without complete response.

5. Dosage regimen: Kymriah intravenous (tisagenlecleucel IV) [must meet both listed below]:

    a. Infuse two to 11 days after completion of lymphodepleting chemotherapy (cyclophosphamide and fludarabine or with bendamustine for cyclophosphamide intolerance or resistance to a previous cyclophosphamide regimen).

    b. Dose 0.6 to 6 x 10^8 CAR-positive viable T cells.

C. Approval:

1. Initial: one time infusion.

2. Re-approval: none.

D. Exclusions:

1. Active infection or inflammatory disorder.

2. Live vaccines: administered within two weeks prior to lymphodepleting chemotherapy.

3. Life expectancy: greater than 12 weeks.

4. Patient performance status (Karnofsky/Lansky): at least 50.

II. Yescarta intravenous (axicabtagene ciloleucel IV).

A. Non-Hodgkin Lymphoma (NHL) [must meet all listed below]:

1. Age: at least 18 years.

2. Prescriber/site: oncologist; Certified Healthcare Facility; training about the management of Cytokine Release Syndrome (CRS) and neurological toxicities.

3. Diagnosis and severity [must meet all listed below]:

a. Large B-cell NHL [must meet one listed below]:

- Diffuse large B-cell lymphoma (DLBCL).
- Primary mediastinal B-cell Lymphoma.
- High grade B-cell lymphoma.
- Diffuse large B-cell lymphoma (DLBCL) arising from follicular lymphoma.

b. CD19 tumor expression.

c. Refractory to therapy or member has had at least two bone marrow relapses.

4. Other therapies: contraindicated, inadequate response, or significant adverse effects to one therapy listed below:

a. Autologous Stem Cell Transplant (SCT): progressed within one year post SCT.

b. Standard chemotherapy: refractory to two lines including anthracycline-based with an anti-CD 20 antibody.

c. Follicular lymphoma transformation to diffuse B-cell lymphoma (DLBCL): refractory to two lines of chemotherapy.

5. Dosage regimen: Yescarta intravenous (axicabtagene ciloleucel IV).

a. Infuse two to 14 days after completion of lymphodepleting chemotherapy (cyclophosphamide and fludarabine).

b. Target dose: 2×10^6 CAR-+ T cells per Kg; maximum dose: 2×10^8 CAR-+ T cells.

6. Approval:

a. Initial: one time infusion.

b. Re-approval: none.

7. Exclusions.

a. History of Allogeneic Stem Cell Transplantation (SCT).

b. Central nervous system disorder: history of presence of seizure disorder, cardiovascular ischemia or hemorrhage, dementia, cerebellar disease, or any autoimmune disease with central nervous system involvement.

c. Active Infection or inflammatory disorder.

d. Pregnancy.

e. Live vaccines: administered within two weeks prior to lymphodepleting chemotherapy.

f. Life expectancy: greater than 12 weeks.

g. Eastern Cooperative Oncology Group (ECOG) performance status: greater than 1.

4.0 Coding:

AFFECTED CODES				
Code	**Brand Name**	**Generic Name**	**Billing Units (1 unit)**	**Prior Approval**
Q2042	Kymriah	tisagenlecleucel	up t 600 million CAR+ t cells	Y
Q2041	Yescarta	axicabta-gene ciloleuce	Up to 200 million CAR+ t cells	Y

5.0 References, Citations, Resources & Associated Documents:

1. Kymriah [package insert] East Hanover, NJ Novartis Pharmaceuticals Corp, October 2020.
2. Yescarta [package insert] Santa Monica, CA; Kite Pharma, Inc. October 2020.
3. Chimeric Antigen Receptor-T cell therapy: Practical considerations for implementation in Europe. HemaSphere, 2018;2:1.

6.0 Appendices:

See pages 5-6.

7.0 Revision History:

Original Effective Date: 06/27/2018

Next Review Date: 11/10/2021

Revision Date	Reason for Revision
9/19	Moved to new format; replaced abbreviations, corrected table
10/20	Annual review; revised criteria instructions and other therapies language; added diagnosis Relapsed or Refractory Diffuse Large B-cell Lymphoma (DLBCL), formatting, approved by P&T Committee 12/9/20

Appendix I: Patient Safety and Monitoring

Drug	Adverse Reactions	Monitoring	REMS
Kymriah Tisagen-lecleucel	• Cardiovascular (CV): hypotension (31%), tachycardia (26%), hypertension (19%) • Central Nervous System (CNS): headache (HA) (37%), brain disease (34%), fatigue (22%), delirium (21%), anxiety (13%), • Endocrine/metabolism: ↓ potassium (27%), ↓Phosphorus (19%) • Gastro intestinal (GI): ↓ appetite, diarrhea (26%), N & V (26%), constipation (18%), abdominal pain (16%) • Hematology/oncology*: anemia (100%), neutropenia (100%), ↓ Platelets, hypogammaglobulinemia (43%), febrile neutropenia (37%), hypofibrinogenemia (16%; with cytokine release syndrome), ↑ INR (13%) • Hepatic*: ↑ AST (28%), ↑ ALT (21%), ↑ bilirubin (21%) • Hypersensitivity: cytokine release syndrome (79%) • Infection: viral (26%), bacterial (19%), fungal (13%) • Musculoskeletal (MSK): limb pain (16%), myalgia (15%), arthralgia (12%) • Renal: acute renal failure (22%) • Respiratory: hypoxia (24%), cough (19%), pulmonary edema (16%), tachypnea (12%) • Miscellaneous: fever (40%) • Pregnancy: animal studies not done, if placental transfer fetal toxicities would occur	• Labs: HBV, HCV and HIV (pre), Immuno-globulins (post), Pregnancy test (pre) • Hypersensitivity: CRS (2-3x 1st wk. & 4 wk. post) • CNS: neurotoxicity (2-3x 1st wk. & 4 wk. post) • Infection • Hematology/oncology: secondary malignancy (life-long)	KYMRIAH REMS. http://www.Kymriah-rems.com/
Yescarta (axicabta-gene ciloleucel)	• CV: hypotension (57%), ↑ HR (57%), cardiac arrhythmia (23%), edema (19%), HTN (15%), thrombosis (10%), cardiac failure (6%), capillary leak syndrome (3%) • CNS: brain disease (57%), fatigue (46%), HA (44-5%), chills (40%), dizziness (21%), motor dysfunction (19%), aphasia (18%), delirium (17%) • Endocrine/metabolism: ↓ Phos. (50%), ↓ Sodium (Na) (19%), weight. loss (16%), ↑ uric acid (13%), dehydration (11%) • GI: ↓ (44%), diarrhea (38%), nausea (34%), vomiting (26%), constipation (23%), abdominal (14%), xerostomia (11%) • Hematology/oncology*: lymphocytopenia (100%), leukopenia (96%), neutropenia (93%), anemia (66%), ↓ Ptls (58%), febrile neutropenia (36%), hypogammaglobulinemia (15%) • Hepatic: ↑ bilirubin (13%) • Hypersensitivity: cytokine release syndrome (94%) • MSK: tremor (31%), limb/back pain (15-7%), myalgia (14%) • Renal: renal insufficiency (12%) • Respiratory: hypoxia (32%), cough (30%), dyspnea (19%), pleural effusion (13%) • Miscellaneous: fever (86%)	• Labs: HBV, HCV and HIV (pre), Immuno-globulins (post), Pregnancy test (pre) • Hypersensitivity: CRS (2-3x 1st wk. & 4 wk. post) • CNS: neurotoxicity (2-3x 1st wk. & 4 wk. post) • Infection • Hematology/oncology: secondary malignancy (life-long)	https://www.yescartarems.com/

Drug	Adverse Reactions	Monitoring	REMS
	• Pregnancy. animal studies not done. if placental transfer fetal toxicities would occur, use not recommended		

**Grade 3 or 4*