BENEFIT COVERAGE POLICY

Title: BCP-77 CAR T-Cell Immunotherapy

Effective Date: 10/01/2018

Physicians Health Plan
PHP Insurance Company
PHP Service Company

Important Information - Please Read Before Using This Policy

The following coverage 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.

Coverage 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:

Health Plan covers CAR T-Cell Immunotherapy when covered services are prior approved.

For all non-network covered services to be paid at the network benefit level except for emergency/urgent services, prior approval is required.

Refer to member's benefit coverage document for specific benefit description, guidelines, coverage, and exclusions.

Unlisted codes are subject to review.

2.0 Background:

Acute leukemia is the most common form of childhood cancer, comprising about 30% of all childhood malignancies. Relapsed and chemotherapy-refractory B-cell acute lymphoblastic leukemia (B-ALL) remain significant causes of cancer-associated morbidity and mortality for children and adults.

Traditional chemotherapy salvage is inadequate and over 50% of patients diagnosed with B-cell ALL develop relapsed or refractory disease. CAR T-Cell Immunotherapy is a novel, immunologic approach where T-cells are genetically engineered to target surface antigens. Severe toxicity (cytokine release syndrome and neurotoxicity) is the primary hurdle to broad implementation of CAR T-Cell Immunotherapy.

On August 30, 2017 CAR T-Cell immunotherapy tisagenlecleucel (Kymriah) was approved by the Food and Drug Administration (FDA) for the treatment of children and young adults with relapsed and/or refractory B-cell acute lymphoblastic leukemia based on an overall remission rate of 82.5%. Two months later a second CAR T-Cell Immunotherapy, axicabtagene ciloleucel (Yescarta) was approved for the treatment of adult patients with relapsed and/or refractory large B-cell (non-Hodgkin) lymphoma based on an objective response rate of 72%.

Kymriah and Yescarta immunotherapy is available at select treatment centers across the United States. View the list of treatment centers at https://www.us.kymriah.com/treatment-center-locator/ or https://www.yescarta.com/centers

3.0 Clinical Determination Guidelines:

Health Plan covers CAR T-Cell Immunotherapy as an inpatient service only with prior approval by the Clinical Pharmacist or Medical Director using the following determination guidelines:

Document the following with chart notes:

A. Kymriah (tisagenlecleucel)

1. Acute Lymphoblastic Leukemia (ALL)

a. Age: three to 25 years.

b. 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) & neurological toxicities.

c. Diagnosis & severity (all below):

i. B-cell Precursor ALL.

ii. CD19 tumor expression.

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

d. Other therapies: Failed, contraindicated or had significant adverse effects (one of the below):

i. Stem Cell Transplant (SCT).

ii. Standard chemotherapy: Two lines without complete response.

iii. Philadelphia Chromosome (PH) +: Two prior lines of tyrosine kinase inhibitor (TKI) therapy (e.g., imatinib, dasatinib, ponatinib).

e. Dosage regimen: Kymriah (tisagenlecleucel).

i. Infuse 2-14 days after completion of lymphodepleting chemotherapy (cyclophosphamide & fludarabine).

ii. Dose:

1) $\leq$50Kg: 0.2 -5 x 10^6 CAR + T cells/kg.

2) >50Kg: 0.1-2.5 10^8 CAR + T cells/Kg.

f. Approval:

i. Initial: x 1 infusion.

ii. Re-approval: None.

g. Exclusions:

i. Active Infection or inflammatory disorder.

ii. Live vaccines: Administered within two weeks prior to lymphodepleting chemotherapy.

iii. Life expectancy: Less than 12 weeks.

iv. Patient performance status (Karnofsky/Lansky): Less than or equal to 50.

B. Yescarta (axicabtagene ciloleucel)

1. Non-Hodgkin Lymphoma (NHL).
    a. Age: At least 18 years.
    b. Prescriber/site: Oncologist; Certified Healthcare Facility; training about the management of Cytokine Release Syndrome (CRS) and neurological toxicities.
    c. Diagnosis and severity (all below).
        i. Large B-cell NHL (one below):
            1) Diffuse large B-cell lymphoma (DLBCL).
            2) Primary mediastinal B-cell Lymphoma.
            3) High grade B-cell lymphoma.
            4) DLBCL arising from follicular lymphoma.
        ii. CD19 tumor expression.
        iii. Refractory to therapy or member has had at least two or more bone marrow relapses.
    d. Other therapies: Failed, contraindicated or had significant adverse effects (one below):
        i. Autologous Stem Cell Transplant (SCT): Progressed within 1-year post SCT.
        ii. Standard chemotherapy: Refractory to two lines including anthracycline-based with an anti-CD 20 antibody.
        iii. Follicular lymphoma transformation to DLBCL: Refractory to two lines of chemotherapy.
    e. Dosage regimen:
        i. Infuse two-14 days after completion of lymphodepleting chemotherapy (cyclophosphamide & fludarabine).
        ii. Target dose: 2×10^6 CAR-+ T cells/Kg; max. dose: 2×10^8 CAR-+ T cells.
    f. Approval:
        i. Initial: x 1 infusion.
        ii. Re-approval: None.
    g. Exclusions.
        i. Allogeneic Stem Cell Transplantation (SCT)
        ii. CNS disorder: History of presence of seizure disorder, CV ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement.
        iii. Active Infection or inflammatory disorder.
        iv. Pregnancy.
        v. Live vaccines: administered within two weeks prior to lymphodepleting chemotherapy.
        vi. Life expectancy: Less than12 weeks.
        vii. Eastern Cooperative Oncology Group (ECOG) performance status: Less than one.

* Grade 3 or 4

C. Appendix I: Patient Safety and Monitoring

Drug	Adverse Reactions	Monitoring	REMS
Kymriah Tisagen-lecleucel	CV: Hypotension (31%), tachycardia (26%), hypertension (19%) CNS: HA (37%), brain disease (34%), fatigue (22%), delirium (21%), anxiety (13%), Endo/metab: ↓K (27%), ↓Phos (19%) GI: ↓Appetite, diarrhea (26%), N & V (26%), constipation (18%), abdominal pain (16%) Hem/Onc*: Anemia (100%), neutropenia (100%), ↓Ptls., 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%) MSK: Limb pain (16%), myalgia (15%), arthralgia (12%) Renal: Acute renal failure (22%) Resp: Hypoxia (24%), cough (19%), pulmonary edema (16%), tachypnea (12%) Misc.: Fever (40%) Preg: Animal studies not done, if placental transfer fetal toxicities would occur	Labs: HBV, HCV and HIV (pre), Immuno-globulins (post), Pregnancy test (pre) Hypersens.: CRS (2-3x 1st wk. & 4 wk. post) CNS: Neurotoxicity (2-3x 1st wk. & 4 wk. post) Infection Hem/onc: 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%) Endo/metab*: ↓Phos. (50%), ↓Na (19%), wgt. loss (16%), ↑uric acid (13%), dehydration (11%) GI: ↓ (44%), diarrhea (38%), nausea (34%), vomiting (26%), constipation (23%), abd. (14%), xerostomia (11%) Hem/Onc.* Lymphocytopenia (100%), leukopenia (96%), neutropenia (93%),	Labs: HBV, HCV and HIV (pre), Immuno-globulins (post), Pregnancy test (pre) Hypersens.: CRS (2-3x 1st wk. & 4 wk. post) CNS: Neurotoxicity (2-3x 1st wk. & 4 wk. post) Infection Hem/onc: Secondary malignancy (life-	https://www.yescartarems.com/

Drug	Adverse Reactions	Monitoring	REMS
	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%) Resp.: Hypoxia (32%), cough (30%), dyspnea (19%), pleural effusion (13%) Misc.: Fever (86%) Preg. Animal studies not done. if placental transfer fetal toxicities would occur, use not recommended	long)	

4.0 Coding:

Prior Approval Legend: Y = All lines of business; N = None required; 1 = HMO/POS; 2 = PPO; 3 = ASO group L0000264; 4 = ASO group L0001269 Non-Union; 5 = ASO group L0001631; 6 = ASO group L0002011; 7 = ASO group L0001269 Union.

COVERED CODES			
Code/ Rev code	**Description**	**Prior Approval**	**Benefit Plan Reference**
Q2040/ 0636	Tisagenlecleucel, up to 250 million CAR-positive viable T-cells, including leukapheresis and dose preparation procedures, per infusion (Kymriah)	Y	Benefits and Coverage: Hospital – Inpatient Stay
Q2041/ 0636	Axicabtagene ciloleucel, up to 200 million autologous anti-CD19 CAR T-cells, including leukapheresis and dose preparation procedures, per infusion (Yescarta)	Y	Benefits and Coverage: Hospital – Inpatient Stay

NON-COVERED CODES		
Code	**Description**	**Benefit Plan Reference/ Reason**

ICD-10 DIAGNOSIS CODES for Kymriah treatment (List all inclusive)	
Code	**Description**
C83.30	Diffuse large B-cell lymphoma, unspecified site
C83.31	Diffuse large B-cell lymphoma, lymph nodes of head, face, and neck
C83.32	Diffuse large B-cell lymphoma, intrathoracic lymph nodes
C83.33	Diffuse large B-cell lymphoma, intra-abdominal lymph nodes
C91.00	Acute myeloblastic leukemia, not having achieved remission
C91.02	Acute myeloblastic leukemia, in relapse

ICD-10 DIAGNOSIS CODES for Yescarta treatment (List all inclusive)	
Code	**Description**
C82.20	Follicular lymphoma grade III, unspecified, unspecified site
C82.21	Follicular lymphoma grade III, unspecified, lymph nodes of head, face and neck
C82.22	Follicular lymphoma grade III, unspecified, intrathoracic lymph nodes
C82.23	Follicular lymphoma grade III, unspecified, intra-abdominal lymph nodes
C82.24	Follicular lymphoma grade III, unspecified, lymph nodes of axilla and upper limb
C82.25	Follicular lymphoma grade III, unspecified, lymph nodes of inguinal region and lower limb
C82.26	Follicular lymphoma grade III, unspecified, intrapelvic lymph nodes
C82.27	Follicular lymphoma grade III, unspecified, spleen
C82.28	Follicular lymphoma grade III, unspecified, lymph nodes of multiple sites
C82.29	Follicular lymphoma grade III, unspecified, extranodal and solid organ sites
C82.30	Follicular lymphoma grade IIIa, unspecified site
C82.31	Follicular lymphoma grade IIIa, lymph nodes of head, face and neck
C82.32	Follicular lymphoma grade IIIa, intrathoracic lymph nodes
C82.33	Follicular lymphoma grade IIIa, intra-abdominal lymph nodes
C82.34	Follicular lymphoma grade IIIa, lymph nodes of axilla and upper limb
C82.35	Follicular lymphoma grade IIIa, lymph nodes of inguinal region and lower limb
C82.36	Follicular lymphoma grade IIIa, intrapelvic lymph nodes
C82.37	Follicular lymphoma grade IIIa, spleen
C82.38	Follicular lymphoma grade IIIa, lymph nodes of multiple sites
C82.39	Follicular lymphoma grade IIIa, extranodal and solid organ sites
C82.40	Follicular lymphoma grade IIIb, unspecified site
C82.41	Follicular lymphoma grade IIIb, lymph nodes of head, face and neck
C82.42	Follicular lymphoma grade IIIb, intrathoracic lymph nodes
C82.43	Follicular lymphoma grade IIIb, intra-abdominal lymph nodes
C82.44	Follicular lymphoma grade IIIb, lymph nodes of axilla and upper limb
C82.45	Follicular lymphoma grade IIIb, lymph nodes of inguinal region and lower limb
C82.46	Follicular lymphoma grade IIIb, intrapelvic lymph nodes
C82.47	Follicular lymphoma grade IIIb, spleen
C82.48	Follicular lymphoma grade IIIb, lymph nodes of multiple sites
C82.49	Follicular lymphoma grade IIIb, extranodal and solid organ sites
C83.30	Diffuse large B-cell lymphoma unspecified site
C83.31	Diffuse large B-cell lymphoma, lymph nodes of head, face, and neck
C83.32	Diffuse large B-cell lymphoma intrathoracic lymph nodes
C83.33	Diffuse large B-cell lymphoma intra-abdominal lymph nodes
C83.34	Diffuse large B-cell lymphoma lymph nodes of axilla and upper limb
C83.35	Diffuse large B-cell lymphoma, lymph nodes of inguinal region and lower limb
C83.36	Diffuse large B-cell lymphoma intrapelvic lymph nodes
C83.37	Diffuse large B-cell lymphoma, spleen
C83.38	Diffuse large B-cell lymphoma lymph nodes of multiple sites
C83.39	Diffuse large B-cell lymphoma extranodal and solid organ sites
C85.20	Mediastinal (thymic) large B-cell lymphoma, unspecified site
C85.21	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of head, face and neck
C85.22	Mediastinal (thymic) large B-cell lymphoma, intrathoracic lymph nodes
C85.23	Mediastinal (thymic) large B-cell lymphoma, intra-abdominal lymph nodes
C85.24	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of axilla and upper limb
C85.25	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of inguinal region and lower limb
C85.26	Mediastinal (thymic) large B-cell lymphoma, intrapelvic lymph nodes

ICD-10 DIAGNOSIS CODES for Yescarta treatment (List all inclusive)	
Code	**Description**
C85.27	Mediastinal (thymic) large B-cell lymphoma, spleen
C85.28	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of multiple sites
C85.29	Mediastinal (thymic) large B-cell lymphoma, extranodal and solid organ sites

5.0 Unique Configuration/Prior Approval/Coverage Details:

None.

6.0 Terms & Definitions:

Acute Lymphoblastic Leukemia (ALL) – the most common childhood cancer in which the bone marrow makes too many immature lymphocytes (a type of white blood cell). This type of cancer gets worse quickly if not treated. ALL can occur in adults with the remission rate lower than that of children. Risk factors include:

- Radiation exposure
- Chemical exposure to hair dyes, benzene, and some chemotherapy drugs

Kymriah – FDA Approved Indication - 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.
- Adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

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

Diffuse Large B-cell Lymphoma (DLBCL) – the most common form of non-Hodgkin lymphoma (NHL) and tends to grow quickly. The cancer starts in the white blood cells called lymphocytes and grows in the lymph nodes, pea-sized glands in the neck, groin, armpits or elsewhere. Treatment usually depends on both the type of lymphoma and stage of the disease. Those at greater risk are:

- Middle-aged or older (average age at time of diagnosis is 64 years old).
- Male.
- Non-Asian or African-American.

Yescarta – FDA Approved Indication - Yescarta is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

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

7.0 References, Citations & Resources:

1. Kymriah [package insert] East Hanover, NJ Novartis Pharmaceuticals Corp, August 2017.
2. Yescarta [package insert] Santa Monica, CA; Kite Pharma, Inc. October 2017.

3. Luskin MR, DeAngelo DJ. Chimeric antigen receptor therapy in acute lymphoblastic leukemia clinical practice. Curr Hematol Malig Rep. June 27, 2017
4. Chimeric Antigen Receptor-T cell therapy: Practical considerations for implementation in Europe. HemaSphere, 2018;2:1.

8.0 Associated Documents [For internal use only]:

Business Process Flow (BPF) – None.

Standard Operating Procedure (SOP) – None.

Desk Level Procedure (DLP) – None.

Sample Letter – None.

Form – None.

Other – None.

9.0 Revision History

Original Effective Date: 10/01/2018

Last Approval Date: 08/15/2018

Next Review Date: 08/08/2019

Revision Date	Reason for Revision
6/18	Policy created.