Pharmacy Benefit Determination Policy

Policy Subject: CAR-T Cell Immunotherapy	**Dates:**
Policy Number: SHS PBD33	**Effective Date:** June 27, 2018
Category: Gene Therapy	**Revision Date**
Policy Type: ☒ **Medical** ☐ **Pharmacy**	**Approval Date:** June 27, 2018
Department: Pharmacy	**Next Review Date:** April 2019
Product (check all that apply):	**Clinical Approval By:**
☒ Group HMO/POS	**Medical Directors**
☒ Individual HMO/POS	PHP: Peter Graham, MD;
☒ PPO	**Pharmacy and Therapeutics Committee**
☒ ASO	PHP: Peter Graham, MD;

Policy Statement:

Physicians Health Plan, PHP Insurance & Service Company, and Sparrow PHP will cover CAR-T Cell Immunotherapy through the Medical Benefit based on approval by the Clinical Pharmacist or Medical Director using the following determination guidelines

Drugs and Applicable Coding:

Q-code: Kymriah - Q2040; Yescarta – Q2041

Clinical Determination Guidelines:

Document the following with chart notes

I. Kymriah (tisagenlecleucel)
   A. Acute Lymphoblastic Leukemia (ALL)
      1. Age: 3-25 yrs.
      2. Prescriber/site: Oncologist; Certified Healthcare Facility enrolled in the Kymriah REMS; training has been given to providers on the management pf cytokine release syndrome (CRS) & neurological toxicities
      3. Diagnosis & severity (all below)
         a. B-cell Precursor ALL
         b. CD19 tumor expression
         c. Refractory to therapy or member has had $\geq$ 2 bone marrow relapses
      4. Other therapies: Failed, contraindicated or had significant adverse effects (one of the below)
         a. Stem Cell Transplant (SCT)
         b. Standard chemotherapy: Two lines without complete response
         c. Philadelphia Chromosome (PH) +: Two prior lines of tyrosine kinas inhibitor (TKI) therapy (e.g. imatinib, dasatinib, ponatinib)
      5. Dosage regimen: Kymriah (tisagenlecleucel)
         a. Infuse 2-14 days after completion of lymphodepleting chemotherapy (cyclophosphamide & fludarabine)
         b. Dose: $\leq$50Kg: 0.2 -5 x 10^6 CAR+ T cells/kg
            >50Kg: 0.1-2.5 10^8 CAR+ T cells/Kg

6. Approval:
   a. Initial: x 1 infusion
   b. Re-approval: None
7. Exclusions:
   a. Active Infection or inflammatory disorder
   b. Live vaccines: Administered within 2 weeks prior to lymphodepleting chemotherapy.
   c. Life expectancy: <12 weeks
   d. Patient performance status (Karnofsky/Lansky): ≤ 50

II. Yescarta (axicabtagene ciloleucel)
A. Non-Hodgkin Lymphoma (NHL)
1. Age: ≥18 yrs.
2. Prescriber/site: Oncologist; Certified Healthcare Facility; training about the management of Cytokine Release Syndrome (CRS) & neurological toxicities.
3. Diagnosis & severity (all below)
   a. Large B-cell NHL (one below)
      - Diffuse large B-cell lymphoma (DLBCL)
      - Primary mediastinal B-cell Lymphoma
      - High grade B-cell lymphoma
      - DLBCL arising from follicular lymphoma
   b. CD19 tumor expression
   c. Refractory to therapy or member has had ≥ 2 bone marrow relapses
4. Other therapies: Failed, contraindicated or had significant adverse effects (one below)
   a. Autologous Stem Cell Transplant (SCT): Progressed within 1-year post SCT
   b. Standard chemotherapy: Refractory to two lines including anthracycline-based with an anti-CD 20 antibody
   c. Follicular lymphoma transformation to DLBCL: Refractory to two lines of chemotherapy
5. Dosage regimen:
   a. Infuse 2-14 days after completion of lymphodepleting chemotherapy (cyclophosphamide & fludarabine)
   b. Target dose: 2×10^6 CAR-+ T cells/Kg; max. dose: 2×10^8 CAR-+ T cells
6. Approval:
   a. Initial: x 1 infusion
   b. Re-approval: None
7. Exclusions
   a. Allogeneic Stem Cell Transplantation (SCT)
   b. CNS disorder: History of presence of seizure disorder, CV ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
   c. Active Infection or inflammatory disorder
   d. Pregnancy
   e. Live vaccines: administered within 2 weeks prior to lymphodepleting chemotherapy
   f. Life expectancy: <12 weeks
   g. Eastern Cooperative Oncology Group (ECOG) performance status: >1

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.Kym riah-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%), 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	• 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)	https://www.yescartarems.com/

**Grade 3 or 4*

References and 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. Chimeric Antigen Receptor-T cell therapy: Practical considerations for implementation in Europe. HemaSphere, 2018;2:1.

Approved By:

6/27/18

Peter Graham, MD – PHP Executive Medical Director — Date

6/27/18

Human Resources (Kurt Batteen) — Date