MEDICAL COVERAGE POLICY
SERVICE: Adoptive Immunotherapy

Policy Number:	**241**
Effective Date:	**01/01/2020**
Last Review:	**10/17/2019**
Next Review Date:	**10/17/2020**

Important note
Unless otherwise indicated, this policy will apply to all lines of business.
Even though this policy may indicate that a particular service or supply may be considered medically necessary and thus covered, this conclusion is not based upon the terms of your particular benefit plan. Each benefit plan contains its own specific provisions for coverage and exclusions. Not all benefits that are determined to be medically necessary will be covered benefits under the terms of your benefit plan. You need to consult the Evidence of Coverage (EOC) or Summary Plan Description (SPD) to determine if there are any exclusions or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and your plan of benefits, the provisions of your benefits plan will govern. However, applicable state mandates will take precedence with respect to fully insured plans and self-funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, Federal mandates will apply to all plans. With respect to Medicare-linked plan members, this policy will apply unless there are Medicare policies that provide differing coverage rules, in which case Medicare coverage rules supersede guidelines in this policy. Medicare-linked plan policies will only apply to benefits paid for under Medicare rules, and not to any other health benefit plan benefits. CMS's Coverage Issues Manual can be found on the CMS website. Similarly, for Medicaid-linked plans, the Texas Medicaid Provider Procedures Manual (TMPPM) supersedes coverage guidelines in this policy where applicable.

SERVICE: Adoptive Immunotherapy

PRIOR AUTHORIZATION: Required. This policy provides guidelines for medical review when that review is NOT performed by vendor Oncology Analytics.

POLICY: Please review the plan's EOC (Evidence of Coverage) or Summary Plan Description (SPD) for coverage details.

For Medicare plans, please refer to appropriate Medicare LCD (Local Coverage Determination). If there is no applicable LCD, use the criteria set forth below.

For Medicaid plans, please confirm coverage as outlined in the Texas Medicaid TMPPM.

Tisagenlecleucel (Kymriah)

SWHP/FirstCare may consider tisagenlecleucel (Kymriah) medically necessary for the treatment of B-cell acute lymphoblastic leukemia (B-ALL) when ALL of the following criteria are met:

1. Member is ≤ 25 years old; **AND**
2. There is documentation of CD19 tumor expression; **AND**
3. The member will be using tisagenlecleucel (Kymriah) at a certified treatment center
4. Member has a performance score on Karnofsky or Lansky Scale of ≥ 50% or Eastern Cooperative Oncology Group (ECOG) performance score is 0-3; **AND**
5. There is now relapsed or refractory disease; **AND EITHER:**
   a. For members of Plans subject to Texas Mandate HB1584: the member has stage 4 advanced metastatic disease; **OR**
   b. The disease is refractory: have failed 2+ cycles of standard chemotherapy, or in second or later relapse; OR member has relapsed/refractory B-ALL as defined by ONE of the following:
      - Second or greater bone marrow (BM) relapse
      - Any BM relapse after allogeneic stem cell transplantation (SCT)
      - Primary refractory (not achieving a complete response after 2 cycles of standard chemotherapy or chemorefractory (not achieving a complete response after 1 cycle of standard chemotherapy for relapsed disease)

- Patients with Philadelphia chromosome (Ph)-positive disease have a contraindication, intolerance, or have failed two prior lines of tyrosine kinase inhibitor (TKI) therapy (e.g., imatinib, dasatinib, ponatinib, etc.).

In addition, the member has or will receive lymphodepleting chemotherapy (Fludarabine 30 mg/m^2 IV daily x 4 days and cyclophosphamide 500mg/m^2 IV daily x 2 days) followed by infusion of Kymriah within 2-14 days of completion of lymphodepleting chemo.

The member will NOT be treated with more than 2.5 x 10^8 viable CAR-T cells AND If the member is less than or equal to 50kg, they will receive weight-based dosing at 0.2-0.5 x 10^6 viable CAR-T cells per kg of body weight.

Member's with the following conditions are NOT eligible for treatment with tisagenlecleucel (Kymriah):

- Active hepatitis B (HBs AG-positive) or active hepatitis C
- Grade 2-4 graft versus host disease
- Active central nervous system (CNS) malignancy involvement (i.e. white blood cell (WBC) count greater than or equal to 5 cells/mcl in the cerebral spinal fluid (CSF) with presence of lymphoblasts
- On immunosuppression for autoimmune disorder/transplant
- Has received prior CD-19 targeted therapy AND/OR prior CD-19 targeted CAR-T cell therapy

Tisagenlecleucel may be considered medically necessary in individuals with large B-cell lymphoma when all of the following criteria in 1 through 6 are met:

1. Member is18 years of age or older; AND
2. There is histologically confirmed diagnosis of one of the following:
    - Diffuse large B-cell lymphoma (DLBCL), not otherwise specified; or
    - High-grade B-cell lymphoma; or
    - Transformed follicular lymphoma; and
3. Member has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and
4. One-time, single administration treatment
5. The member will be receiving treatment at a certified treatment center
6. There is now relapsed or refractory disease; **AND EITHER:**
    a. For members of Plans subject to Texas Mandate HB1584: the member has stage 4 advanced metastatic disease; **OR**
    b. There is relapsed or refractory disease defined as progression after two or more lines of systemic therapy (which may or may not include therapy supported by autologous stem cell transplant); AND member must have received adequate prior therapy including at least one of the following:
        - An anthracycline-containing chemotherapy regimen and rituximab; or
        - Either failed autologous hematopoietic stem cell transplantation (ASCT), were ineligible for or refused consent to ASCT; and

SWHP/FirstCare considers repeat administration of tisagenlecleuce experimental and investigational because the effectiveness of this strategy has not been established.

SWHP/FirstCare considers tisagenlecleucel to be experimental and investigational for all other indications.

Members with the following conditions are NOT eligible for treatment with tisagenlecleucel (Kymriah):

- Active hepatitis B (HBs AG-positive) or active hepatitis C
- Grade 2-4 graft versus host disease
- Active central nervous system (CNS) malignancy involvement (i.e. white blood cell (WBC) count greater than or equal to 5 cells/mcl in the cerebral spinal fluid (CSF) with presence of lymphoblasts
- On immunosuppression for autoimmune disorder/transplant
- Has received prior CD-19 targeted therapy AND/OR prior CD-19 targeted CAR-T cell therapy

Axicabtagene (Yescarta)

SWHP/FirstCare may consider axicabtagene (Yescarta) medically necessary when the following criteria are met:

1. The member has a diagnosis of large B-cell lymphoma [i.e. diffuse large B-cell lymphoma (DBLCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma for which member has received chemotherapy]; **AND**
2. The member is ≥ 18 years of age; **AND**
3. The member will be using axicabtagene (Yescarta) at a certified treatment center.
4. The member has relapsed or refractory disease, **AND EITHER:**
   a. For members of Plans subject to Texas Mandate HB1584: the member has stage 4 advanced metastatic disease; **OR**
   b. Received two or more prior lines of systemic therapy with both an anthracycline containing chemotherapy regimen and anti-CD20 monoclonal antibody, unless tumor is CD-20 negative, AND has relapsed or refractory disease defined as one of the following:
      - Progressive disease or stable disease relapsing in less than or equal to 6 months; OR
      - Disease progression or recurrence less than or equal to 12 months after prior autologous stem cell transplant (ASCT);
      - If salvage therapy is given post-ASCT, member did not have response to, or relapsed after, the last line of therapy;

AND: In addition, the member has or will receive lymphodepleting chemotherapy (Fludarabine 30 mg/m^2 IV daily x 3 days and cyclophosphamide 500mg/m^2 IV daily x 3 days) followed by infusion of Yescarta within 2-14 days of completion of lymphodepleting chemo.

Member's with the following conditions are **NOT** eligible for treatment with axicabtagene (Yescarta):

- Active hepatitis B (HBs AG-positive) or active hepatitis C, or any uncontrolled infection
- CNS disease including primary CNS lymphoma
- Grade 2-4 graft versus host disease if status-post allo-transplant
- On immunosuppression therapy for autoimmune disease/transplant
- Has received prior CD-19 targeted therapy AND/OR prior CD-19 targeted CAR-T cell therapy

SWHP/FirstCare considers repeat administration of axicabtagene (Yescarta) experimental and investigational because the effectiveness of this strategy has not been established.

SWHP/FirstCare considers axicabtagene (Yescarta) to be experimental and investigational for the following diagnoses secondary to paucity of safety and efficacy data (not all-inclusive list):

a. Adults and Pediatric acute lymphoblastic leukemia
b. Acute Myeloid Leukemia
c. Follicular Lymphoma
d. Non-Hodgkin's Lymphoma - indolent
e. Multiple myeloma
f. Mantle Cell Lymphoma
g. Primary central nervous system lymphoma.

OVERVIEW

Chimeric antigen receptor (CAR) T cells and genetically engineered T-cell receptor (TCR T) cells are manufactured by collecting lymphocytes from a patient or donor and modifying them using gene transfer techniques. Viral vectors are introduced that express cell receptors that are highly specific for tumor antigens. CAR T and TCR T cells are then infused back into the patient, where they direct a targeted immune response to cancerous tissue. CAR T cells express a hybrid receptor with an extracellular single-chain antibody fragment, a transmembrane domain, and at least 1 intracellular signaling domain. CAR T cells are most often used to treat hematological malignancies, and a common target is B-cell cluster of differentiation antigen 19 (CD19)

The U. S. Food and Drug Administration (FDA) approved the Biologics License Application (BLA) for Kymriah (tisagenlecleucel) (Novartis Pharmaceuticals Corp.) on August 30, 2017 for the treatment of patients up to 25 years of age with B-Cell precursor acute lymphoblastic leukemia (B-ALL) that is refractory or in second or later relapse. The boxed warning includes the clarification that Kymriah is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) because of the risk of CRS and neurological toxicities. See the official drug insert for details.

In a pivotal phase 2 study published by Maude et al (ref 35), a single infusion of tisagenlecleucel provided durable remission with long-term persistence in pediatric and young adult patients with relapsed or refractory B-cell ALL, with transient high-grade toxic effects. The overall remission rate within 3 months was 81%, with all patients who had a response to treatment found to be negative for minimal residual disease. It should be noted that the cytokine release syndrome occurred in 77% of patients and neurologic events occurred in 40% of patients (managed with supportive care).

A study from Memorial Sloan Kettering Cancer Center looked at long-term data in adults with relapsed/refractory B-cell ALL (ref 36). There were 53 adults in the cohort. The median follow-up was 29 months (range: 1-65), the median event-free survival among the 53 treated patients was 6.1 months and the median overall survival was 12.9 months. Complete Remission was observed in 83% of patients.

In a 2016 comprehensive review, Holtzinger et al. (2016) list over 100 ongoing clinical trials evaluating CAR T cells with a variety of targets for a variety of indications. Most of the trials are underway in the United States or Canada, and about a quarter of the trials are underway in China. They also allude to 7 completed phase I trials on CAR T cells for hematological malignancy. The authors conclude that more research is needed to identify ideal CAR T cell targets, receptor designs, and lymphodepletion regimens; control toxic effects like CRS; and evaluate the use of CAR T cells with HSCT (Holzinger et al., 2016)

National Comprehensive Cancer Network (NCCN) gives Tisagenlecleucel, for relapsed or refractory B-ALL for patients ≤ 25 years with refractory disease or ≥ 2 relapses and failure of 2 tyrosine kinase inhibitors (TKIs), a recommendation category of 2A.

Although early results look promising, based on review of available information, SWHP/FirstCare has determined Tisagenlecleucel experimental with insufficient data demonstrating safety and long-term efficacy.

Yescarta (Axicabtagene ciloleucel) is an autologous CAR T-cell therapy, a novel type of immunotherapy in which a patient's own genetically altered immune cells are used to attack cancer cells.

The U. S. Food and Drug Administration (FDA) approved the Biologics License Application (BLA) for Yescarta (axicabtagene ciloleucel) (Kite Pharma Inc.) on October 18, 2017 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. This drug label contains the same boxed warning stating that Yescarta is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).

The objective response rate was 82%, and the complete response rate was 54%.With a median follow-up of 15.4 months, 42% of the patients continued to have a response, with 40% continuing to have a complete response. The overall rate of survival at 18 months was 52%.

The pivotal trial (ZUMA) that lead to approval was a phase 2 trial with 111 patients. Among the 111 patients who were enrolled, axi-cel was successfully manufactured for 110 (99%) and administered to 101 (91%). The objective response rate was 82%, and the complete response rate was 54%.With a median follow-up of 15.4 months, 42% of the patients continued to have a response, with 40% continuing to have a complete response. The overall rate of survival at 18 months was 52%. Grade 3 or higher cytokine release syndrome and neurologic events occurred in 13% and 28% of the patients, respectively. Three of the patients died during treatment.

National Comprehensive Cancer Network (NCCN) gives Yescarta (Axicabtagene ciloleucel), for subsequent therapy for transformed Follicular Lymphoma, diffuse large B-cell lymphoma, AIDs-related B-cell lymphomas, & Posttransplant Lymphoproliferative Disease a recommendation category of 2A.

Although early results look promising, based on review of available information, SWHP/FirstCare has determined Axicabtagene experimental with insufficient data demonstrating safety and long-term efficacy.

CODES:

Important note:
CODES: Due to the wide range of applicable diagnosis codes and potential changes to codes, an inclusive list may not be presented, but the following codes may apply. Inclusion of a code in this section does not guarantee that it will be reimbursed, and patient must meet the criteria set forth in the policy language.

CPT Codes:	36511 Therapeutic apheresis; for white blood cells
CPT Not Covered:	
HCPCS	Q2042 - Kymriah (Tisagenlecleucel) Q2041 - Yescarta (Axicabtagene ciloleucel)

	S2107 Adoptive immunotherapy i.e., development of specific an-tumor reactivity (e.g., tumor-infiltrating lymphocyte therapy) per course of treatment
ICD10 codes:	
ICD10 Not covered:	

CMS:

POLICY HISTORY:

Status	Date	Action
New	10/24/2017	New policy
Update	12/13/2017	Added newly assigned code for Kymriah effective 1/1/18
Update	04/03/2018	Codes for Kymriah and Yescarta added. Coverage criteria added along with PA requirement.
Review	02/26/2019	Code update
Review	04/25/2019	Criteria updated and review process altered to include OA
Update	10/17/2019	Updated to include Texas HB 1584 language
	06/29/2020	Logo changed to include FC

REFERENCES:

The following scientific references were utilized in the formulation of this medical policy. SWHP will continue to review clinical evidence related to this policy and may modify it at a later date based upon the evolution of the published clinical evidence. Should additional scientific studies become available and they are not included in the list, please forward the reference(s) to SWHP so the information can be reviewed by the Medical Coverage Policy Committee (MCPC) and the Quality Improvement Committee (QIC) to determine if a modification of the policy is in order.

1. Almåsbak H, Aarvak T, Vemuri MC. CAR T cell therapy: a game changer in cancer treatment. J Immunol Res. 2016;2016:5474602.
2. Brentjens RJ. Are chimeric antigen receptor T cells ready for prime time? Clin Adv Hematol Oncol. 2016;14(1):17-19.
3. Brudno JN, Somerville RP, Shi V, et al. Allogeneic T cells that express an anti-CD19 chimeric antigen receptor induce remissions of B-cell malignancies that progress after allogeneic hematopoietic stem-cell transplantation without causing graft-versus-host disease. J Clin Oncol. 2016;34(10):1112-1121.
4. Children's Hospital of Philadelphia (CHOP). What to Expect: CAR T-cell Therapy Process. 2017. Available at: http://www.chop.edu/centers-programs/cancer-immunotherapy-program/your-experience. Accessed August 8, 2017.
5. Fitzgerald JC, Weiss SL, Maude SL, et al. Cytokine release syndrome after chimeric antigen receptor T cell therapy for acute lymphoblastic leukemia. Crit Care Med. 2017;45(2):e124-e131.
6. Gardner RA, Finney O, Annesley C, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. Blood. 2017;129(25):3322-3331.
7. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol. 2010;28(27):4184-4190.
8. Harris DT, Kranz DM. Adoptive T cell therapies: a comparison of T cell receptors and chimeric antigen receptors. Trends Pharmacol Sci. 2016;37(3):220-230.
9. Hettle R, Corbett M, Hinde S, et al. The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. Health Technol Assess. 2017;21(7):1-204.

10. Holzinger A, Barden M, Abken H. The growing world of CAR T cell trials: a systematic review. Cancer Immunol Immunother. 2016;65(12):1433-1450.
11. Ikeda H. T-cell adoptive immunotherapy using tumor-infiltrating T cells and genetically engineered TCR-T cells. Int Immunol. 2016;28(7):349-353.
12. Inman S. Juno Accelerates Development of JCAR017, Halts JCAR015. March 2, 2017. Available at: http://www.onclive.com/web-exclusives/juno-accelerates-development-of-jcar017-halts-jcar015. Accessed August 8, 2017.
13. Kebriaei P, Singh H, Huls MH, et al. Phase I trials using Sleeping Beauty to generate CD19-specific CAR T cells. J Clin Invest. 2016;126(9):3363-3376.
14. Kochenderfer JN, Somerville RPT, Lu T, et al. Lymphoma remissions caused by anti-CD19 chimeric antigen receptor T cells are associated with high serum interleukin-15 levels. J Clin Oncol. 2017;35(16):1803-1813.
15. Lee DW, Kochenderfer JN, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet. 2015;385(9967):517-528.
16. Leukemia and Lymphoma Society (LLS). Chimeric Antigen Receptor (CAR) T-Cell Therapy. 2017. Available at: https://www.lls.org/treatment/types-of-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy.
17. Locke FL, Davila ML. Regulatory challenges and considerations for the clinical application of CAR-T cell anti-cancer therapy. Expert Opin Biol Ther. 2017;17(6):659-661.
18. Locke FL, Neelapu SS, Bartlett NL, et al. Phase 1 results of ZUMA-1: a multicenter study of KTE-C19 anti-CD19 CAR T cell therapy in refractory aggressive lymphoma. Mol Ther. 2017;25(1):285-295.
19. Lymphoma Research Foundation (LRF). Diffuse Large B-Cell Lymphoma (DLBCL). 2016. Available at: http://www.lymphoma.org/site/pp.asp?c=bkLTKaOQLmK8E&b=6300153. Accessed August 8, 2017.
20. Martin A, Morgan E, Hijiya N. Relapsed or refractory pediatric acute lymphoblastic leukemia: current and emerging treatments. Paediatr Drugs. 2012;14(6):377-387.
21. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014;371(16):1507-1517.
22. Maus MV, Nikiforow S. The why, what, and how of the new fact standards for immune effector cells. J Immunother Cancer. 2017;5:36.
23. Pan J, Yang JF, Deng BP, et al. High efficacy and safety of low-dose CD19-directed CAR-T cell therapy in 51 refractory or relapsed B acute lymphoblastic leukemia patients. Leukemia. 2017. Epub ahead of print. May 15, 2017. Available at: http://www.nature.com/leu/journal/vaop/ncurrent/full/leu2017145a.html?foxtrotcallback=true. Accessed August 8, 2017.
24. Rapoport AP, Stadtmauer EA, Binder-Scholl GK, et al. NY-ESO-1-specific TCR-engineered T cells mediate sustained antigen-specific antitumor effects in myeloma. Nat Med. 2015;21(8):914-921.
25. Rose S. DLBCL responds well to anti-CD19 CAR therapy. Cancer Discov. 2017;7(3):241-242.
26. Sehn LH, Gascoyne RD. Diffuse large B-cell lymphoma: optimizing outcome in the context of clinical and biologic heterogeneity. Blood. 2015;125(1):22-32.

27. Turtle CJ, Hanafi LA, Berger C, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest. 2016a;126(6):2123-2138.
28. Turtle CJ, Hanafi LA, Berger C, et al. Immunotherapy of non-Hodgkin's lymphoma with a defined ratio of CD8+ and CD4+ CD19-specific chimeric antigen receptor-modified T cells. Sci Transl Med. 2016b;8(355):355ra116.
29. Turtle CJ, Hay KA, Hanafi LA, et al. Durable molecular remissions in chronic lymphocytic leukemia treated With CD19-specific chimeric antigen receptor-modified T cells after failure of ibrutinib. J Clin Oncol. 2017:JCO2017728519. Epub ahead of print. July 17, 2017. Available at: http://ascopubs.org/doi/abs/10.1200/JCO.2017.72.8519?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed&. Accessed August 8, 2017.
30. Ye B, Stary CM, Gao Q, et al. Genetically modified T-cell-based adoptive immunotherapy in hematological malignancies. J Immunol Res. 2017;2017:5210459.
31. Zhang T, Cao L, Xie J, et al. Efficiency of CD19 chimeric antigen receptor-modified T cells for treatment of B cell malignancies in phase I clinical trials: a meta-analysis. Oncotarget. 2015;6(32):33961-33971.
32. Locke FL, Neelapu SS, Bartlett NL, Siddiqi T, Chavez JC, Hosing CM, Ghobadi A, Budde LE, Bot A, Rossi JM, Jiang Y, Xue AX, Elias M, Aycock J, Wiezorek J, Go WY. Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma. Mol Ther. 2017 Jan 4;25(1):285-295. doi: 10.1016/j.ymthe.2016.10.020. Epub 2017 Jan 4.
33. Locke FL, et. al. Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma.
34. Zachary J. Roberts, Marc Better, Adrian Bot, Margo R. Roberts & Antoni Ribas (2017): Axicabtagene ciloleucel, a first-in-class CAR T cell therapy for aggressive NHL, Leukemia & Lymphoma, DOI: 10.1080/10428194.2017.1387905
35. Maude SL, Laetsch TW, et al. Tisagenlecleucel in children and young adults with B-Cell Lymphoblastic Leukemia. N Engl J Med. 2018;378(5):439-448. Pubmed 29385370
36. Riviere I, et. al. Long-term follow-up of CD19 CAR therapy in Acute Lymphoblastic Leukemia. N Engl J Med. 2018;378(5):449-459.
37. Neelapu SS, Locke FL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med. 2017;377:2531-2544