CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Brexucabtagene Autoleucel (Tecartus®)

Version: 1.0

EFFECTIVE DATE: 1/1/2024

NantHealth® | Eviti®

Please note the following:

Brexucabtagene Autoleucel (Tecartus®)

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

Note: For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Brexucabtagene Autoleucel (Tecartus): Discussion

Acute lymphoblastic leukemia (ALL) is a heterogenous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs. The age-adjusted incidence rate of ALL in the US is 1.8 per 100,000 individuals per year, with approximately 5,690 new cases and 1,580 deaths estimated in 2021. The median age at diagnosis for ALL is 17 years with 53.5% of patients diagnosed at younger than 20 years of age. In contrast, 29.6% of cases are diagnosed at 45 years or older and only approximately 13.7% of patients are diagnosed at 65 years or older. ALL represents 75% to 80% of acute leukemias among children, making it the most common form of childhood leukemia; by contrast**,** acute lymphoblastic leukemia represents approximately 20% of all leukemias among adults. Brexucabtagene autoleucel is the second CAR T-cell therapy for adult patients with relapsed or refractory B-ALL. [1]

Mantle cell lymphoma (MCL) comprises about 3% of all newly diagnosed cases of non-Hodgkin's lymphomas (NHL). MCL is thought to possess the unfavorable characteristics of both indolent and aggressive NHL subtypes owing to the incurability of disease with conventional chemotherapy and a typically more aggressive disease course compared to indolent lymphomas. MCL is characterized by the reciprocal chromosomal translocation t(11;14), juxtaposing the cyclin D1 locus with the immunoglobulin heavy chain (IGH) gene locus, resulting in the overexpression of cyclin D1 and the diagnosis of MCL generally requires the expression of cyclin D1. It is rare to have a diagnosis of cyclin D1 negative disease, occurring only in less than 5% of patients. The pathologic features and clinical characteristics of cyclin D1 negative MCL appear to be like those of cyclin D1 positive MCL and thus, they are treated the same. [2]

Currently, available CAR-T therapies are customized for each individual patient. They are made by collecting T cells from the patient and re-engineering them in the laboratory to produce proteins on their surface called chimeric antigen receptors, or CARs. The CARs recognize and bind to specific proteins, or antigens, on the surface of the cancer cells. After the revamped T cells are expanded into the millions in the laboratory, they are infused back into the patient. The CAR-T cells will continue to multiply in the patient's body and, with guidance from their engineered receptor, recognize and kill any cancer cells that harbor the target antigen on their

surfaces. Brexucabtagene autoleucel is a CD19-directed genetically modified autologous T-cell immunotherapy. Brexucabtagene autoleucel was granted accelerated approval by the FDA for relapsed and refractory mantle cell lymphoma (MCL) on July 24, 2020. On October 1, 2021, Brexucabtagene autoleucel received approval for adult patients with relapsed and refractory B-cell precursor acute lymphoblastic leukemia. [3]

Due to complications from CAR-T therapies of Cytokine Release Syndrome (CRS) and neurologic deficits, all providers/healthcare facilities involved in the treatment of patients getting brexucabtagene autoleucel, must be registered in the brexucabtagene autoleucel (Tecartus) Risk Evaluation and Mitigation Strategy (REMS) program. [4]

In the multicenter, phase 2 trial, relapsed/refractory mantle cell lymphoma patients were evaluated to assess a primary endpoint of the percentage of patients with an objective response with secondary endpoints of the duration of response, progression-free survival, and overall survival. The results of the study showed a 93% objective response with 67% having a complete response. For secondary endpoints, the progression-free and overall survival at 12 months was 61% and 83% respectively. In the primary efficacy analysis, 78% of those that had a complete response were continuing to have a response after a median follow-up time of 12.3 months. [5]

In the phase II, Zuma-3 study for ALL, the primary endpoints resulted in complete remission or complete remission with incomplete haematological recovery. Secondary endpoints were duration of response, relapse-free survival, overall survival, minimal residual disease (MRD) negativity rate, and allogeneic stem cell transplantation (allo-SCT) rate. At the medium follow-up of 16.4 months, 71% of patients had complete remission or complete remission with incomplete haematological recovery, with 56% of patients reaching complete remission. The median duration of remission was 12.8 months, median relapse-free survival was 11.6 months in all patients, and 14.2 months in responders. The median overall survival was 18.2 months. Among responders, the median overall survival was not reached, and 97% of patients had MRD negativity. Allo-SCT consolidation was given to 18% of patients. [6]

Brexucabtagene Autoleucel: Definitions

- **Cytokine Release Syndrome- (CRS)-** A life-threatening complication of CAR-T therapy that occurred in 91% of patients receiving brexucabtagene autoleucel for MCL, including ≥ Grade 3 in 18% of patients. CRS occurred in 92% of patients with ALL, including ≥ Grade 3 CRS in 26% of the patients. The median time to onset of CRS was 3 days and the median duration of CRS was 10 days for patients with MCL. The median time to onset of CRS was 5 days and the median duration of CRS was 8 days for patients with ALL. The key manifestations of CRS (>10%) we similar in MCL and ALL and included fever (93%), hypotension (62%), tachycardia (59%), chills (32%), hypoxia (31%), headache (21%), fatigue (20%) and nausea (13%). [4]
- **Food and Drug Administration (FDA)-** The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs,

biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.

- **National Comprehensive Cancer Network (NCCN)-** An alliance of thirty-two leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated and Nanthealth, Inc. reviews these and updates its policies within a timely manner.
- **Neurologic Toxicities-** Brain and nervous system events, including those that were fatal or life-threatening, have occurred following treatment with brexucabtagene autoleucel. Brain and nervous system events occurred in 81% of patients with MCL in clinical trials, including ≥ Grade 3 in 37% of the patients. Brain and nervous system events occurred in 87% of patients with ALL, including ≥ Grade 3 in 35% of the patients. The most common brain and nervous system events (>10%) were similar in MCL and ALL and included encephalopathy (57%), headache (37%), tremors (34%), confusional state (26%), aphasia (23%), delirium (17%), dizziness (15%), anxiety (14%), and agitation (12%). The median time for onset of brain and nervous system events was 6 days with a median range of twenty-one days in patients with MCL. For ALL, the median time for the onset of brain and nervous system events was 7 days with a median duration of fifteen days. [4]
- **Risk Evaluation and Mitigation Strategy (REMS) -** A drug safety program to manage known or potential risks associated with a drug(s) and is required by the US Food and Drug Administration (FDA) to ensure that the benefits of a drug outweigh its risks. The REMS program for brexucabtagene autoleucel is also the REMS program for axicabtagene ciloleucel. These therapies are only available through this restricted program. The program ensures that hospitals and their associated clinic(s) that dispense brexucabtagene autoleucel or axicabtagene ciloleucel are specially certified and have on-site, immediate access to a minimum of two doses of tocilizumab. The program also ensures that those who prescribe, dispense, or administer brexucabtagene autoleucel are aware of how to manage the risks of CRS and neurologic toxicities. Those involved in the program must successfully complete the knowledge assessment and submit it to the REMS Program. [4]

Brexucabtagene Autoleucel: Policy

Brexucabtagene Autoleucel will be considered for coverage when the following criteria are met:

Mantle Cell Lymphoma:

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Healthcare facility/provider has enrolled in the axicabtagene ciloleucel and brexucabtagene autoleucel REMS program; AND

4. Previously received an anthracycline - or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a Bruton tyrosine kinase inhibitor (BTKi, ibrutinib or acalabrutinib); AND
5. Has a diagnosis of relapsed or refractory mantle cell lymphoma (MCL) (only given after chemoimmunotherapy and Bruton tyrosine kinase inhibitor (BTKi]) described as:
   a) No response or progressive disease following second-line therapy with covalent Bruton tyrosine kinase inhibitor (BTKI) or other continuous treatment regimens i.e., lenalidomide and rituximab.
   b) Partial response, no response, or progressive disease following second-line therapy with fixed-duration regimens.
   c) Relapsed disease (relapse number two or greater) following second-line therapy (if not previously given; AND
5. An ECOG performance status of 0-1; AND
6. Has not had any of the following:
   a) Central nervous system (CNS) lymphoma
   b) History of allogenic stem cell transplantation
   c) Prior chimeric antigen receptor (CAR) therapy or other genetically modified T-cell therapy; AND
7. Screened for hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV); AND
8. Will receive a lymphodepleting chemotherapy regimen of cyclophosphamide and fludarabine per physician discretion; AND

Dosage:

The target dose is 2×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 CAR-positive viable T cells.

For reauthorization:

Brexucabtagene autoleucel is a one-time dose and will not be renewed.

Acute Lymphoblastic Leukemia

For authorization:

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Has relapsed/refractory (R/R) B-cell precursor acute lymphoblastic leukemia (ALL) defined as ONE of the following:
   a) Primary refractory disease
   b) First relapse if remission lasted ≤ 12 months.
   c) Relapsed or refractory after 4 or more lines of therapy.
   d) Relapsed or refractory following therapy that has included TKI's if the individual's ALL is Philadelphia chromosome-positive

   e) Relapsed or refractory ALL at least 100 days post allogeneic stem cell transplantation (HSCT); AND
4. Has documented CD19 tumor expression; AND
5. Has an ECOG performance of 0 or 1; AND
6. Has been screened for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV); AND
7. Will receive a lymphodepleting chemotherapy regimen once the brexucabtagene autoleucel is ready. This regimen of cyclophosphamide and fludarabine is per the physician's discretion.

Dosage:

The dose of brexucabtagene autoleucel is given at a target dose of 1×10^6 anti-CD19 CAR T cells/kg (maximum 1×10^8 cells).

Note: Coverage of brexucabtagene autoleucel will be provided for FDA-approved indications or National Comprehensive Cancer Network (NCCN) guidelines when it is a Category 1, 2A, or 2B recommendation OR when all criteria are met.

For reauthorization:

Brexucabtagene autoleucel is a one-time dose and will not be renewed.

Brexucabtagene autoleucel: References

1. National Comprehensive Cancer Network Guidelines. Acute Lymphoblastic Leukemia (Version 1.2022). http://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed April 20, 2023.
2. National Comprehensive Cancer Network Guidelines. B-Cell Lymphomas (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed April 20, 2023
3. CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers. https://www.cancer.gov/about-cancer/treatment/research/car-t-cells/. Accessed April 20, 2023.
4. Risk Evaluation and Mitigation Strategy (REMS). www.yescartatecartusrems.com. Accessed April 20, 2023.
5. Wang et al, N Engl J Med 382:1331-42;2020. KTE-X19 for Relapsed or Refractory Adult B-cell Acute Lymphoblastic Leukaemia: Phase 2 Results of the Single-arm, Open-label, Multicentre ZUMA-3 Study. https://pubmed.ncbi.nlm.nih.gov/32242358/. Accessed April 20, 2023.
6. Shah et al, Lancet 398:491–502;2021. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. https://pubmed.ncbi.nlm.nih.gov/34097852/. Accessed April 20, 2023.

Brexucabtagene Autoleucel: Coding (ICD 10 and HCPCS) *

*Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment. CPT codes are available through the AMA.

CODE	DESCRIPTION
C83.10-C83.19	Mantle Cell Lymphoma
C91.00 and C91.02	Acute lymphoblastic leukemia
Q2053	Brexucabtagene autoleucel, up to 200 million autologous anti-cd19 car positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose
XW033M7	Introduction of brexucabtagene0537T autoleucel immunotherapy into peripheral vein, percutaneous approach, new technology group 7
XW043M7	Introduction of brexucabtagene autoleucel immunotherapy into central vein, percutaneous approach, new technology group 7
0537T	Chimeric antigen receptor T-cell (CAR-T) therapy; harvesting of blood-derived T lymphocytes for development of genetically modified autologous CAR-T cells, per day
0538T	Chimeric antigen receptor T-cell (CAR-T) therapy; preparation of blood-derived T lymphocytes for transportation (e.g., cryopreservation, storage)
0539T	Chimeric antigen receptor T-cell (CAR-T) therapy; receipt and preparation of CAR-T cells for administration
0540T	Chimeric antigen receptor T-cell (CAR-T) therapy; CAR-T cell administration, autologous
0871	Cell Collection w/CPT code 0537T
0872	Specialized Biologic Processing and Storage – Prior to Transport w/CPT 0538T
0873	Storage and Processing after Receipt of Cells from Manufacturer w/CPT 0539T
0874	Infusion of Modified Cells w/CPT 0540T
0891	Special Processed Drugs – FDA Approved Cell Therapy – Charges for Modified cell therapy

Brexucabtagene Autoleucel: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	1/1/2024
2	Policy Review Dates:	5/26/2023
3	Policy Revision Dates:	
4	Department Owner:	Medical Affairs
5	NH Advisory Committee Approval Dates:	6/16/2023
6	Revision Changes:	