BlueCross BlueShield of Arizona
An Independent Licensee of the Blue Cross and Blue Shield Association

MEDICAL COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 08/27/18
LAST REVIEW DATE:
LAST CRITERIA REVISION DATE:
ARCHIVE DATE:

YESCARTA™ (axicabtagene ciloleucel)

Non-Discrimination Statement and Multi-Language Interpreter Services information are located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Medical Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Medical Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Medical Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Medical Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

YESCARTA (axicabtagene ciloleucel) (cont.)

Description:

Chimeric antigen receptor T (CAR T) cells are a form of genetically modified autologous immunotherapy that can be directed at B cell lymphoma. This customized treatment uses the individual's own T lymphocytes, which are genetically modified (transfected) with a gene that encodes a chimeric antigen receptor to direct the individual's T cells against the lymphoma cells. The T cells are genetically modified ex-vivo, expanded in a production facility, and then infused back into the individual as therapy.

Yescarta is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adults 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.

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of cancers originating in B-lymphocytes, T-lymphocytes or natural killer cells. Diffuse large B cell lymphoma (DLBCL) is the most common subtype of NHL. First line therapy for DLBCL includes an anthracycline-containing regimen combined with rituximab (for example, RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone).

In individuals who relapse after first line therapy, the goal of second line therapy is to achieve a response that will make the individual eligible for autologous stem cell transplant (ASCT). Second-line therapy for transplant-eligible individual includes rituximab and combination chemotherapy (for example, RICE (rituximab, ifosfamide, carboplatin and etoposide) and RDHAP (rituximab, dexamethasone, cytarabine and cisplatin)). Refractory DLBCL may be defined as progressive disease (PD) or stable disease (SD) as the best response at any point during chemotherapy (> 4 cycles of first-line or 2 cycles of later-line therapy) or as relapse 12 or fewer months after autologous cell transplantation.

Primary mediastinal B cell lymphoma (PMBCL) has distinct clinical, pathological, and molecular characteristics compared to DLBCL. PMBCL is thought to arise from thymic (medullary) B-cells and represents approximately 3% of individuals diagnosed with DLBCL. Initial therapy of PMBCL includes anthracycline-containing regimens in combination with rituximab with or without radiotherapy.

Follicular lymphoma (FL), a B-cell lymphoma, is the most common indolent (slow-growing) form of NHL, accounting for approximately 20-30% of all NHLs. Some individuals with FL will transform (TFL) histologically to DLBCL which is more aggressive and associated with a poor outcome. Initial treatment of TFL is influenced by prior therapies for FL but includes anthracycline-containing regimens in combination with rituximab.

Treatment options for relapsed/refractory PMBCL and TFL are similar to those in DLBCL.

YESCARTA (axicabtagene ciloleucel) (cont.)

Definitions:

Adult: Age 18 years and older

Relapsed or Refractory Disease: progression after 2 or more lines of systemic therapy (which may or may not include therapy supported by autologous cell transplant).

Chemotherapy-Refractory Disease:
One or more of the following: no response to first-line therapy (primary refractory disease) or no response to second or greater lines of therapy or disease progression or relapse within 12 months of autologous stem cell transplant.

Risk Evaluation and Mitigation Strategies (REMS):
Use of Yescarta is subject to a Risk Evaluation and Mitigation Strategies (REMS) program that requires provider, patient, and dispensing pharmacy be enrolled into the program. Only providers and Pharmacies enrolled into the REMS may prescribe and dispense the drug, respectively, to individuals who are also in the program. A REMS program attempts to manage known or potentially serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) for some drugs to ensure that the benefits of a drug outweigh its risks.

The required components of the Yescarta REMS are:
- Healthcare facilities that dispense and administer Yescarta must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of two doses of tocilizumab are available for each individual for infusion within 2 hours after Yescarta infusion, if needed for treatment of Cytokine Release Syndrome (CRS).
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer Yescarta are trained about the management of CRS and neurologic toxicities.

Further information is available at www.YescartaREMS.com or 1-844-454-KITE (5483).

YESCARTA (axicabtagene ciloleucel) (cont.)

Criteria:

For gene therapy with Kymriah, refer to BCBSAZ Medical Coverage Guideline #O1037, *"Kymriah (tisagenlecleucel)".*

For gene therapy other than Kymriah and Yescarta, refer to BCBSAZ Medical Coverage Guideline #O680, *"Gene Therapy".*

For adoptive immunotherapy and chimeric antigen receptor T (CAR T) cell immunotherapy other than Kymriah, refer to BCBSAZ Medical Coverage Guideline #O368, *"Immunotherapy, Adoptive".*

Yescarta will be reviewed by the medical director(s) and clinical pharmacist(s).

See Resources section for FDA-approved dosage, Anthracycline and Anti-CD 20 Monoclonal Antibody Agents Table.

YESCARTA IS AVAILABLE ONLY THROUGH A RESTRICTED PROGRAM UNDER A RISK EVALUATION AND MITIGATION STRATEGY (REMS) CALLED THE YESCARTA REMS PROGRAM.

YESCARTA (axicabtagene ciloleucel) (cont.)

Criteria: (cont.)

- Yescarta is considered ***medically necessary*** for treatment of relapsed or refractory large B-cell lymphoma with documentation of **ALL** of the following:

1. 18 years of age or older
2. Histologically confirmed diagnosis of **ONE** of the following:
   - Diffuse large B-cell lymphoma (DLBCL), not otherwise specified
   - Diffuse large B-cell lymphoma arising from transformed follicular lymphoma
   - Primary mediastinal large B-cell lymphoma
   - High-grade B-cell lymphoma
3. Chemotherapy-refractory disease as defined by **ONE** or more of the following:
   - No response to first-line therapy (primary refractory disease) as defined by **ONE** of the following:
     a. Progressive disease (PD) as best response to first line therapy
     b. Stable disease (SD) as best response after at least 4 cycles of first line therapy with SD duration no longer than 6 months from last dose of therapy
   - No response to second line therapy as defined by **ONE** or more of the following:
     a. Progressive disease (PD) as best response to first line therapy
     b. Stable disease (SD) as best response after at least 2 cycles of the last line therapy with SD duration no longer than 6 months from last dose of therapy
   - Disease progression or relapse $\leq$ 12 months post-autologous stem cell transplantation with biopsy proven recurrence in relapse individuals
4. Received adequate prior therapy including **ALL** of the following:
   - Anti-CD20 monoclonal antibody for CD20-positive tumor
   - Anthracycline containing chemotherapy regimen
   - For individuals with transformed follicular lymphoma, must have received prior chemotherapy for follicular lymphoma and subsequently have chemotherapy refractory disease after transformation to diffuse large B-cell lymphoma

YESCARTA (axicabtagene ciloleucel) (cont.)

Criteria: (cont.)

- Yescarta is considered ***medically necessary*** for treatment of relapsed or refractory large B-cell lymphoma with documentation of **ALL** of the following: (cont.)

  5. **ALL** of the following:

     - Absolute neutrophil count ≥ 1000/µL
     - Absolute lymphocyte count > 100/µL
     - Platelet count ≥ 75,000/µL

  6. Individual has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis
  7. Individual has not received prior treatment with axicabtagene ciloleucel or any other gene therapy or is being considered for treatment with any other gene therapy
  8. There is evidence of CD19 tumor expression
  9. Individual does not have any clinically significant active systemic fungal, bacterial, viral, or other infection that is uncontrolled or requires intravenous antimicrobials for management
  10. Individual has not received vaccination with live virus vaccines at least 6 weeks prior to the start of lymphodepleting chemotherapy, will not receive live virus vaccines during treatment and before immune recovery following treatment with Yescarta

- Yescarta for all other indications not previously listed or if above criteria not met is considered ***experimental or investigational*** based upon:

  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

  These indications include, *but are not limited to:*

  - Treatment with dosing or frequency outside the FDA-approved dosing and frequency

YESCARTA (axicabtagene ciloleucel) (cont.)

Resources:

Literature reviewed 08/27/18. We do not include marketing materials, poster boards and non-published literature in our review.

The BCBS Association Medical Policy Reference Manual (MPRM) policy is included in our guideline review. References cited in the MPRM policy are not duplicated on this guideline.

1. 8.01.01 BCBS Association Medical Policy Reference Manual. Adoptive Immunotherapy. Re-issue date 07/12/2018, issue date 12/01/1996.

2. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) B-cell Lymphomas Version 7. 2017. 12/05/2017.

3. National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium. Axicabtagene ciloleucel. Accessed 12/27/2017.

4. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N Engl J Med.* Dec 28 2017;377(26):2531-2544.

5. Neelapu SS LF, Bartlett NL, et al.,. Supplement to: Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N Engl J Med.* 2017;377(26):2531-2544.

6. Neelapu SS LF, Bartlett NL, et al.,. Protocol for: Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N Engl J Med.* 2017;377(26):2531-2544.

YESCARTA (axicabtagene ciloleucel) (cont.)

Resources: (cont.)

Yescarta Package Insert:

- FDA-approved indication and dosage:

Indication	Recommended Dose
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. Pregnancy status of females with reproductive potential should be verified. Sexually-active females of reproductive potential should have a pregnancy test prior to starting treatment. YESCARTA is not recommended for women who are pregnant, and pregnancy after YESCARTA infusion should be discussed with the treating physician.	For autologous use and intravenous use only. Each single infusion bag of YESCARTA contains a suspension of chimeric antigen receptor (CAR)-positive T cells in approximately 68 mL. 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. Do not use a leukodepleting filter. Administer a lymphodepleting regimen of cyclophosphamide and fludarabine before infusion of YESCARTA. Verify the patient's identity prior to infusion. Premedicate with acetaminophen and an H1-antihistamine. Treat severe or life-threatening Cytokine Release Syndrome (CRS) with tocilizumab or tocilizumab and corticosteroids Confirm availability of tocilizumab prior to infusion. Administer YESCARTA in a certified healthcare facility.

Initial Approval:
Approve 1 unit of Yescarta (axicabtagene), up to 2×10^8 CAR-positive viable T cells, including leukapheresis and dose preparation procedures, per infusion for a one-time treatment course per lifetime

Renewal Information:
Continued therapy will not be authorized as Yescarta (axicabtagene) is indicated to be dosed one time only.

YESCARTA (axicabtagene ciloleucel) (cont.)

Resources: (cont.)

Anthracycline and Anti-CD 20 Monoclonal Antibody Agents Table

Anthracycline Agents	Anti-CD 20 Monoclonal Antibody Agents
Adriamycin (doxorubicin hydrochloride, conventional)	Gazyva (obinutuzumab)
Doxil or Lipodox 50 (doxorubicin hydrochloride, liposomal (pegylated liposomal doxorubicin))	Rituxan (rituximab)
Mitoxantrone – anthracenedione, related to anthracyclines	Rituxan hycela (rituximab/hyaluronidase)
	Zevalin Y-90 (ibritumomab tiuxetan)

YESCARTA (axicabtagene ciloleucel) (cont.)

Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html

Multi-Language Interpreter Services:

Spanish: Si usted, o alguien a quien usted está ayudando, tiene preguntas acerca de Blue Cross Blue Shield of Arizona, tiene derecho a obtener ayuda e información en su idioma sin costo alguno. Para hablar con un intérprete, llame al 602-864-4884.

Navajo: Díí kwe'é atah nílínigíí Blue Cross Blue Shield of Arizona haada yit'éego bína'ídíłkidgo éí doodago Háida bíjá anilyeedígíí t'áadoo le'é yína'ídíłkidgo beehaz'áanii hóló díí t'áá hazaadk'ehjí háká a'doowołgo bee haz'ą doo bąąh ílínígóó. Ata' halne'ígíí kojį' bich'į' hodíilnih 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於插入項目的名稱 Blue Cross Blue Shield of Arizona 方面的問題，您有權利免費以您的母語得到幫助和訊息。洽詢一位翻譯員，請撥電話 在此插入數字 877-475-4799。

Vietnamese: Nếu quý vị, hay người mà quý vị đang giúp đỡ, có câu hỏi về Blue Cross Blue Shield of Arizona quý vị sẽ có quyền được giúp và có thêm thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thông dịch viên, xin gọi 877-475-4799.

Arabic:
إن كان لديك أو لدى شخص تساعده أسئلة بخصوص Blue Cross Blue Shield of Arizona، فلديك الحق في الحصول على المساعدة والمعلومات الضرورية بلغتك من دون اية تكلفة. للتحدث مع مترجم اتصل ب 877-475-4799.

YESCARTA (axicabtagene ciloleucel) (cont.)

Multi-Language Interpreter Services: (cont.)

Tagalog: Kung ikaw, o ang iyong tinutulangan, ay may mga katanungan tungkol sa Blue Cross Blue Shield of Arizona, may karapatan ka na makakuha ng tulong at impormasyon sa iyong wika ng walang gastos. Upang makausap ang isang tagasalin, tumawag sa 877-475-4799.

Korean: 만약 귀하 또는 귀하가 돕고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona 에 관해서 질문이 있다면 귀하는 그러한 도움과 정보를 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 그렇게 통역사와 얘기하기 위해서는 877-475-4799 로 전화하십시오.

French: Si vous, ou quelqu'un que vous êtes en train d'aider, a des questions à propos de Blue Cross Blue Shield of Arizona, vous avez le droit d'obtenir de l'aide et l'information dans votre langue à aucun coût. Pour parler à un interprète, appelez 877-475-4799.

German: Falls Sie oder jemand, dem Sie helfen, Fragen zum Blue Cross Blue Shield of Arizona haben, haben Sie das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Um mit einem Dolmetscher zu sprechen, rufen Sie bitte die Nummer 877-475-4799 an.

Russian: Если у вас или лица, которому вы помогаете, имеются вопросы по поводу Blue Cross Blue Shield of Arizona, то вы имеете право на бесплатное получение помощи и информации на вашем языке. Для разговора с переводчиком позвоните по телефону 877-475-4799.

Japanese: ご本人様、またはお客様の身の回りの方でも、Blue Cross Blue Shield of Arizona についてご質問がございましたら、ご希望の言語でサポートを受けたり、情報を入手したりすることができます。料金はかかりません。通訳とお話される場合、877-475-4799 までお電話ください。

Farsi:
اگر شما، یا کسی که شما به او کمک میکنید ، سوال در مورد Blue Cross Blue Shield of Arizona ، داشته باشید حق این را دارید که کمک و اطلاعات به زبان خود را به طور رایگان دریافت نمایید 877-475-4799
.]تماس حاصل نمایید.

Assyrian:
ܒ ܫܟܚ، ܡ ܣ ܩܙܝܩܐ ܘܣܝܥܐ ܒܗ، ܫܐܠܬܐ ܚܕܐ ܕܡܬܐ ܚܕܐ ܒܗ، ܫܟܚ ܫܐܠܬܐ ܕܡܬܐ ܚܕܐ ،Blue Cross Blue Shield of Arizona
ܝܘܬܐ ܘܥܘܕܪܢܐ ܕܟܬܒܐ ܒܠܫܢܟ. ܟܐܒܪܐ ܟܬ ܣ ܐܚܕ ܕܐ ܒܠܫܢ ܐ ܒܗ ܟܬ ܐܟܐ ܒܗ ܕܒ ܐܝܬ 877-475-4799.

Serbo-Croatian: Ukoliko Vi ili neko kome Vi pomažete ima pitanje o Blue Cross Blue Shield of Arizona, imate pravo da besplatno dobijete pomoć i informacije na Vašem jeziku. Da biste razgovarali sa prevodiocem, nazovite 877-475-4799.

Thai: หากคณ หรอคนทคณกาลงชวยเหลอมคาถามเกยวกบ Blue Cross Blue Shield of Arizona
คณมสทธทจะไดรบความชวยเหลอและขอมลในภาษา ของคณไดโดยไมมคาใชจาย พดคยกบลาม โทร 877-475-4799