

DRUG DETERMINATION POLICY

Title: DDP-38 CAR-T Cell Immunotherapy

Effective Date: 12/13/23



Physicians Health Plan
PHP Insurance Company
PHP Service Company

Important Information - Please Read Before Using This Policy

The following 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.

Benefit 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 situation.

Contact PHP Customer Service to discuss plan benefits more specifically.

1.0 Policy:

This policy describes the determination process for coverage of specific drugs.

This policy does not guarantee or approve benefits. Coverage depends on the specific benefit plan. Drug Determination Policies are not recommendations for treatment and should not be used as treatment guidelines.

2.0 Background or Purpose:

CAR-T cell immunotherapy is covered through the medical benefit based on approval by the Health Plan after review by a clinical pharmacist and the medical director. These criteria were developed and implemented to ensure appropriate use for the intended diagnoses and mitigation of toxicity, if possible.

3.0 Clinical Determination Guidelines:

Document the following with chart notes:

I. General Considerations

A. Appropriate medication use [must meet all listed below]:

1. Diagnosis: meets standard diagnostic criteria that designate signs, symptoms, and test results to support specific diagnosis.
2. FDA approval status [must meet one listed below]:
 - a. FDA approved: product, indication, and/or dosage regimen.
 - b. Non-FDA approved: compendium support (Lexicomp™, NCCN) for the use of a drug for a non-FDA-approved indication or dosage regimen.
3. Place in therapy: sequence of therapy supported by national or international accepted guidelines and/or studies (e.g., oncologic, infectious conditions).

- B. Prescriber/site: oncologist; Certified Healthcare Facility enrolled in the specific CAR-T REMS; training has been given to providers on the management of cytokine release syndrome (CRS) and neurological toxicities.
- C. Approval:
 - 1. Initial: one-time infusion.
 - 2. Re-approval: none.
- D. Exclusions [meets one listed below]:
 - 1. History of Allogeneic Stem Cell Transplantation (SCT), unless otherwise stated.
 - 2. Central nervous system disorder: history of seizure disorder, cardiovascular ischemia or hemorrhage, dementia, cerebellar disease, or any autoimmune disease with central nervous system involvement.
 - 3. Active Infection or inflammatory disorder.
 - 4. Pregnancy.
 - 5. Live vaccines: administered within two weeks prior to lympho-depleting chemotherapy.
 - 6. Life expectancy: less than 12 weeks.

II. Kymriah intravenous (tisagenlecleucel IV).

- A. Acute Lymphoblastic Leukemia [must meet all listed below]:
 - 1. Age: three to 25 years.
 - 2. Diagnosis and severity [must meet all listed below]:
 - a. B-cell Precursor Acute Lymphoblastic Leukemia (ALL).
 - b. CD19 tumor expression.
 - c. Refractory to therapy or member has had at least two bone marrow relapses.
 - 3. Other therapies: A trial of one therapeutic category listed below is required unless all are contraindicated. Trial must result in an inadequate response or severe adverse reaction.
 - a. Autologous Stem Cell Transplant (SCT).
 - b. Standard chemotherapy: two lines without complete response.
 - c. Philadelphia chromosome-positive: two prior lines of tyrosine kinase inhibitor (TKI) therapy (e.g., imatinib, dasatinib, ponatinib).
 - 4. Dosage regimen: Kymriah intravenous (tisagenlecleucel IV).
 - a. Infuse two to 14 days after completion of lymphodepleting chemotherapy (cyclophosphamide and fludarabine).
 - b. Dose: less than 50kg: $0.2 - 5 \times 10^6$ CAR+ T cells per kg.; greater than 50kg: $0.1-2.5 \times 10^8$ CAR+ T cells per kg.
- B. Relapsed or Refractory Diffuse Large B-cell Lymphoma (DLBCL) [must meet all listed below]:
 - 1. Age: at least 18 years.
 - 2. Diagnosis and severity [must meet one listed below]:
 - a. High-grade B-cell Lymphoma.
 - b. DLBDL arising from follicular lymphoma.

- c. DLBL not otherwise specified.
- 3. Other therapies: A trial of one therapeutic category listed below is required unless all are contraindicated. Trial must result in an inadequate response or severe adverse reaction.
 - a. Autologous Stem Cell Transplant (SCT).
 - b. Standard chemotherapy: two lines without complete response.
- 4. Dosage regimen: Kymriah intravenous (tisagenlecleucel IV) [must meet both listed below]:
 - a. Infuse two to 11 days after completion of lymphodepleting chemotherapy (cyclophosphamide and fludarabine or with bendamustine for cyclophosphamide intolerance or resistance to a previous cyclophosphamide regimen).
 - b. Dose 0.6 to 6 x 10⁸ CAR-positive viable T cells.

III. Yescarta intravenous (axicabtagene ciloleucel IV).

- A. Large B-cell Non-Hodgkin Lymphoma (NHL) with CD 19 tumor expression [must meet all listed below]:
 - 1. Age: at least 18 years.
 - 2. Diagnosis and severity [must meet all listed below]:
 - a. Diffuse large B-cell lymphoma (DLBCL).
 - b. Primary mediastinal B-cell Lymphoma.
 - c. High-grade B-cell lymphoma.
 - d. Diffuse large B-cell lymphoma (DLBCL) arising from follicular lymphoma.
 - 3. Other therapies: A trial of one therapeutic category listed below is required unless all are contraindicated. Trial must result in an inadequate response or severe adverse reaction.
 - a. Autologous Stem Cell Transplant (SCT): progressed within one year post SCT.
 - b. Standard chemotherapy: refractory to two lines, including anthracycline-based with an anti-CD 20 antibody.
 - c. Follicular lymphoma transformation to diffuse B-cell lymphoma (DLBCL): refractory to two lines of chemotherapy.
 - 4. Dosage regimen: Yescarta intravenous (axicabtagene ciloleucel IV).
 - a. Infuse two to 14 days after completion of lymphodepleting chemotherapy (cyclophosphamide and fludarabine).
 - b. Target dose: 2 x 10⁶ CAR-+ T cells per Kg; maximum dose: 2 x 10⁸ CAR-+ T cells.

IV. Breyanzi intravenous (lisocabtageme maraleucel IV).

- A. Relapsed or Refractory Diffuse Large B-cell Lymphoma (DLBCL) [must meet all listed below]:
 - 1. Age: at least 18 years.
 - 2. Diagnosis and severity [must meet one listed below]:
 - a. High-grade B-cell Lymphoma.
 - b. Follicular lymphoma grade 3B.
 - c. Primary mediastinal large B-cell lymphoma.
 - d. DLBL not otherwise specified (including DLBCL arising from indolent lymphoma).

3. Other therapies: A trial of one therapeutic category listed below is required unless all are contraindicated. Trial must result in an inadequate response or severe adverse reaction.
 - a. Autologous and/or Allogeneic Stem Cell Transplant (SCT).
 - b. Standard chemotherapy: two lines without complete response.
 4. Dosage regimen: Breyanzi intravenous (lisocabtageme maraleucel IV).
 - a. Infuse two to seven days after completion of three days of lymphodepleting chemotherapy (cyclophosphamide and fludarabine).
 - b. Dose 50 to 110 x 10⁶ CAR-T positive viable T cells.
- V. Tecartus intravenous (brexucabtagene autoleucel IV).
- A. Refractory mantle cell lymphoma.
1. Age: at least 18 years.
 2. Diagnosis and severity.
 - a. Refractory treatment or in second or later relapse.
 - b. CD19-positive in the latest relapse as confirmed by immunohistochemistry or flow cytometry.
 - c. The member has not received any prior FDA-approved CD19-directed therapy (e.g., Tecartus, Kymriah, or Yescarta).
 - d. The member has adequate organ and bone marrow function as determined by the treating oncologist or hematologist.
 3. Other therapies: trials of one therapy from each group listed below are required unless contraindicated. Trials must result in an inadequate response or severe adverse reaction.
 - a. Tyrosine kinase inhibitor (BTKI) such (e.g., Ibrutinib, Acalabrutinib, Zanubrutinib).
 - b. The member has previously received Anti-CD20 monoclonal antibody therapy (e.g., rituximab, obinutuzumab).
 - c. Anthracycline- or benamustine-containing chemotherapy.
 4. Dosage regimen:
 - a. Infuse two to four days after completion of chemotherapy (with fludarabine and cyclophosphamide).
 - b. Target dose: 2 x 10⁶ CAR-positive viable T cells per kg body weight (Wang 2020); maximum dose: 2 x 10⁸ CAR-positive viable T cells.
- B. Acute Lymphoblastic Leukemia (ALL) [must meet all listed below]:
1. Age: at least 18 years.
 2. Diagnosis and severity [must meet all listed below]:
 - a. B-cell Precursor ALL.
 - b. CD19 tumor expression.
 - c. Refractory to therapy or member has had at least two bone marrow relapses.
 3. Other therapies: a trial of at least one therapy below is required unless all are contraindicated. Trials must result in an inadequate response or severe adverse reaction.
 - a. Allogenic Stem Cell Transplant (SCT).

- b. Standard chemotherapy: two lines without complete response.
 - c. Philadelphia chromosome positive: two prior lines of tyrosine kinase inhibitor (TKI) therapy (e.g., imatinib, dasatinib, ponatinib).
4. Dosage regimen: Tecartus intravenous (brexucabtagene autoleucl IV).
- a. Infuse two to four days after completion of chemotherapy (with fludarabine and cyclophosphamide).
 - b. Target dose: 2×10^6 CAR-positive viable T cells per kg body weight (Wang 2020); maximum dose: 2×10^8 CAR-positive viable T cells.

VI. Abecma intravenous (Idecabtagene Vicleucl IV) and Carvykti (ciltacabtagene autoleucl).

A. Multiple myeloma [must meet all listed below]:

1. Age: at least 18 years.
2. Diagnosis and severity.
 - a. Diagnosis: relapsed or refractory multiple myeloma without known central nervous system involvement.
3. Other therapies: Trials of at least four therapies listed below are required unless contraindicated. Trials must result in an inadequate response or severe adverse reaction:
 - a. Immunomodulatory agent (e.g., thalidomide, pomalidomide, lenalidomide).
 - b. Proteasome inhibitor (e.g., isatuximab or daratumumab).
 - c. Anti-CD38 monoclonal antibody (e.g., ixazomib, bortezomib, or carfilzomib).
4. Dosage regimen:
 - a. Infuse two days after completion of chemotherapy (with fludarabine and cyclophosphamide).
 - b. Abecma intravenous (Idecabtagene Vicleucl IV): Target dose: 300 to 460×10^6 CAR-positive viable T-cells. Delay icleucl infusion up to seven days for unresolved serious adverse events.
 - c. Carvykti (ciltacabtagene autoleucl): $0.5\text{-}1.0 \times 10^6$ CAR-positive viable T-cells per kg body weight, with a maximum dose of 1×10^8 CAR+ viable T cells per one-time infusion.

4.0 Codes:

COVERED CODES AND PRODCUTS				
Code	Brand Name	Generic Name	Billing Units (1 unit)	Prior Approval
Q2042	Kymriah	tisagenlecleucl	Up t 600 million CAR+ t cells	Y
Q2041	Yescarta	axicabta-gene ciloleuce	Up to 200 million CAR+ t cells	Y
Q2056	Carvykti	ciltacabtagene autoleucl	Up to 100 million CAR+ t cells	Y

COVERED CODES AND PRODCUTS				
Code	Brand Name	Generic Name	Billing Units (1 unit)	Prior Approval
Q2054	Breyanzi	Lisocabtagene maraeucl	Up to 110 million CAR+ t cells	Y
Q2055	Abecma	Idecabtagene Vicleuce	Up to 460 million CAR+ t cells	Y
Q2053	Tecartus	brexucabtagene autoleucl	Up to 200 million CAR+ t cells	Y

5.0 References, Citations, Resources & Associated Documents:

1. Kymriah [package insert] East Hanover, NJ Novartis Pharmaceuticals Corp, October 2022.
2. Yescarta [package insert] Santa Monica, CA; Kite Pharma, Inc. October 2020.
3. Chimeric Antigen Receptor-T cell therapy: Practical considerations for implementation in Europe. HemaSphere, 2018;2:1.
4. Lexi comp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc. Kymriah, Yescarta, Breyanzi, Tecartus, Abcema accessed October 2022.
5. Management of immune-related adverse events in patients treated with chimeric antigen Receptor T-Cell therapy: ASCO Guideline. Journal of Clinical Oncology Nov 2021 <https://ascopubs.org/doi/full/10.1200/JCO.21.01992>
6. Carvykti [package insert]. Horsham, PA: : Janssen Biotech, Inc.; 2023.

6.0 Appendices:

See pages 8-10.

7.0 Revision History:

Original Effective Date: 06/27/2018

Next Review Date: 11/10/2024

Revision Date	Reason for Revision
9/19	Moved to new format; replaced abbreviations, corrected table
10/20	Annual review; revised criteria instructions and other therapies language; added diagnosis Relapsed or Refractory Diffuse Large B-cell Lymphoma (DLBCL), formatting, approved by P&T Committee 12/9/20
3/21	Off cycle review, added Breyanzi; approved at 4/28/21 P&T
10/21	Annual review; added drugs Tecartus and Abecma; reformatted, deleted ECOG performance status as exclusion, clarified life expectancy exclusion
10/22	Annual review; added reference
9/23	Annual Review; added Carvykti in line with PDL, clarified autologous vs allogenic stem cell transplant, updated formatting, updated coding section for Breyanzi, Abecma, and Tecartus, updated other therapies language, clarified four lines of therapy require for Abecma and Carvykti, added that review for these agents is by a clinical pharmacist and the medical director.

Appendix I: Patient Safety and Monitoring

Drug	Adverse Reactions	Monitoring	REMS
<p>Kymriah Tisagen- lecleucel</p>	<ul style="list-style-type: none"> • Cardiovascular: hypotension (31%), tachycardia (26%), hypertension (19%) • Central Nervous System (CNS): headache (37%), brain disease (34%), fatigue (22%), delirium (21%), anxiety (13%), • Endocrine/Metabolism: decreased potassium (27%), decreased phosphorus (19%) • Gastrointestinal (GI): decreased appetite, diarrhea (26%), nausea and vomiting (26%), constipation (18%), abdominal pain (16%) • Hematology/Oncology*: anemia (100%), neutropenia (100%), decreased platelets, hypogammaglobinemia (43%), febrile neutropenia (37%), 003 (16%; with cytokine release syndrome), increased INR (13%) • Hepatic: increased liver function tests (28-21%), increased bilirubin (21%) • Hypersensitivity: cytokine release syndrome (79%) • Infection: viral (26%), bacterial (19%), fungal (13%) • Musculoskeletal: limb pain (16%), myalgia (15%), arthralgia (12%) • Renal: acute renal failure (22%) • Respiratory: hypoxia (24%), cough (19%), pulmonary edema (16%), tachypnea (12%) • Miscellaneous: fever (40%) • Pregnancy: animal studies not done, if placental transfer fetal toxicities would occur 	<ul style="list-style-type: none"> • Labs: HBV, HCV and HIV (pre), Immuno-globulins (post), pregnancy test (pre) • Hypersensitivity: cytokine release syndrome (2-3x first week and 4 weeks post) • Central Nervous System: neurotoxicity (2-3x first week and 4 weeks post) • Infection • Hematology/Oncology: secondary malignancy (life-long) 	<p>KYMRIAH REMS. http://www.Kymriah-rems.com/</p>
<p>Yescarta (axicabta- gene cicleucel)</p>	<ul style="list-style-type: none"> • Cardiovascular: hypotension (57%), increased heart rate (57%), cardiac arrhythmia (23%), edema (19%), hypertension (15%), thrombosis (10%), cardiac failure (6%), capillary leak syndrome (3%) • Central Nervous System: brain disease (57%), fatigue (46%), headache (44-5%), chills (40%), dizziness (21%), motor dysfunction (19%), aphasia (18%), delirium (17%) • Endocrine/Metabolism: decreased phosphorus. (50%), decreased sodium (19%), weight loss (16%), increased uric acid (13%), dehydration (11%) • Gastrointestinal: decreased appetite (44%), diarrhea (38%), nausea (34%), vomiting (26%), constipation (23%), abdominal (14%), xerostomia (11%) • Hematology/Oncology*: lymphocytopenia (100%), leukopenia (96%), neutropenia (93%), anemia (66%), decreased platelets (58%), febrile neutropenia (36%), hypogammaglobinemia (15%) • Hepatic: increased bilirubin (13%) • Hypersensitivity: cytokine release syndrome (94%) • Musculoskeletal: tremor (31%), limb/back pain (15-7%), myalgia (14%) • Renal: renal insufficiency (12%) • Respiratory: hypoxia (32%), cough (30%), dyspnea (19%), pleural effusion (13%) • Miscellaneous: fever (86%) • Pregnancy. animal studies not done. if placental transfer fetal toxicities would occur, use not recommended 		<p>https://www.yescartarems.com/</p>

Drug	Adverse Reactions	Monitoring	REMS
Breyanzi intravenous Lisocabtagene maraleucel IV	<ul style="list-style-type: none"> • Cardiovascular: edema (21%), hypertension (14%), hypotension (26%), tachycardia (25%) • Dermatological: skin rash (13%) • Endocrine/Metabolism: hypophosphatemia (grades 3 to 4 - 13%) • Gastrointestinal: abdominal pain (21%), constipation (23%), decreased appetite (28%), diarrhea (26%), nausea (33%), vomiting (21%) • Hematology/Oncology: anemia (grades 3/4: 23%), hyperfibrinogenemia (grades 3/4: 15%), hypogammaglobinemia (32%), neutropenia (grades 3/4: 76%), thrombocytopenia (grades 3/4: 39%) • Hypersensitivity: cytokine release syndrome (46%) • Immunologic: antibody development (11%) • Infection: bacterial infection (13%), infection (29%) • Nervous System: chills (12%), dizziness (24%), encephalopathy (29%), fatigue (48%), headache (30%), insomnia (14%), neurological signs and symptoms (35%), peripheral neuropathy (11%) • Neuromuscular & Skeletal: musculoskeletal pain (37%) • Renal: renal failure syndrome (11%) • Respiratory: cough (23%), dyspnea (16%), upper respiratory tract infection (13%) • Miscellaneous: fever (16%) 		https://www.BreyanziREMS.com
Abecma Idecabtagene Vicleucel	<ul style="list-style-type: none"> • Cardiovascular: edema (25%), hypertension (11%), hypotension (17%), tachycardia (19%) • Dermatologic: skin rash (14%), xeroderma (11%) • Endocrine & Metabolic: hypophosphatemia (grades 3/4: 45%), weight loss (13%) • Gastrointestinal: constipation (16%), decreased appetite (22%), diarrhea (35%), nausea (29%), vomiting (15%) • Hematologic & Oncologic (grades 3 or 4): anemia (63%), febrile neutropenia (16%), hypogammaglobinemia (21% to 41%; leukopenia (96%), lymphocytopenia (92%), neutropenia (96%), thrombocytopenia (63%) • Hypersensitivity: cytokine release syndrome (85%) • Immunologic: antibody development (47%) • Infection: bacterial infection (15%), infection (51% to 70%; serious infection: 19%), viral infection (27%) • Nervous System: anxiety (12%), chills (11%), dizziness (17%), encephalopathy (26%), fatigue (45%), headache (23%), insomnia (13%), motor dysfunction (11%), mouth pain (12%), neurotoxicity (28%), peripheral neuropathy (17%) • Neuromuscular & Skeletal: musculoskeletal pain (45%) • Respiratory: cough (23%), dyspnea (13%), pneumonia (17%), upper respiratory tract infection (34%) • Miscellaneous: fever (25%), physical health deterioration (11%) 		https://www.abecmarems.com/

Drug	Adverse Reactions	Monitoring	REMS
Tecartus Brexucabtagene Autoleucel	<ul style="list-style-type: none"> • Cardiovascular: edema (35%), hypertension (18%), hypotension (57%), tachycardia (45%), thrombosis (17%) • Dermatologic: skin rash (9% to 22%) • Endocrine & Metabolic: hypocalcemia (21%), hyponatremia (16%), hypophosphatemia (grade 3/4: 30%), increased uric acid (17%) • Gastrointestinal: abdominal pain (17%), constipation (29%), decreased appetite (26%), diarrhea (28%), nausea (35%), vomiting (13%) • Genitourinary: decreased urine output (11%) • Hematologic & Oncologic: anemia (55%), hypogammaglobinemia (16%), leukopenia (95%), lymphocytopenia (86%), neutropenia (95%), thrombocytopenia (63%) • Hepatic: increased serum alanine aminotransferase (15%), increased serum aspartate aminotransferase (grade 3/4: 15%) • Hypersensitivity: cytokine release syndrome (91%) • Infection: bacterial infection (13%), infection (43% to 56%; including severe infection), viral infection (18%) • Nervous System: anxiety (16%), aphasia (20% to 23%), chills (41%), delirium (16% to 18%), dizziness (18%), encephalopathy (51%), fatigue (48%), headache (35%), insomnia (21%), motor dysfunction (17%), mouth pain (16%), neuropathy (13%), neurotoxicity (81%), pain (17%) • Neuromuscular & Skeletal: musculoskeletal pain (37%), tremor (38%) • Renal: renal insufficiency (18%) • Respiratory: cough (38%), dyspnea (24%), hypoxia (40%), pleural effusion (21%) • Miscellaneous: fever (94%) 		https://www.yescartatecartusrems.com/

*Grade 3 or 4