

# DRUG DETERMINATION POLICY

**Title:** DDP-38 CAR-T Cell Immunotherapy

**Effective Date:** 12/15/2021



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 particular 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. 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 designates 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 use of a drug for a non-FDA approved indication or dosage regimen.
  - c. 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).
2. Central nervous system disorder: history of presence 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: contraindicated, inadequate response or significant adverse effects to one of the therapies below:
  - a. 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: contraindicated, inadequate response or significant adverse effects to one of the therapies below:
  - a. 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 10<sup>8</sup> 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. Prescriber/site: oncologist; Certified Healthcare Facility; training about the management of Cytokine Release Syndrome (CRS) and neurological toxicities.
3. 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.
4. Other therapies: contraindicated, inadequate response, or significant adverse effects to one therapy listed below:
  - 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.
5. Dosage regimen: Yescarta intravenous (axicabtagene ciloleucel IV).
- a. Infuse two to 14 days after completion of lymphodepleting chemotherapy (cyclophosphamide and fludarabine).
  - b. Target dose:  $2 \times 10^6$  CAR-+ T cells per Kg; maximum dose:  $2 \times 10^8$  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: contraindicated, inadequate response or significant adverse effects to one of the therapies below:
  - a. 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  $110 \times 10^6$  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 to treatment or in second or later relapse. B.
  - 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) 1.
  - c. The member has adequate organ and bone marrow function as determined by the treating oncologist or hematologist.

3. Other therapies: contraindicated, inadequate response or significant adverse effects to one of each listed below]:
  - a. Tyrosine kinase inhibitor (BTKI) such (e.g., Ibrutinib, Acalabrutinib, Zanubrutinib. E.
  - 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:  $2 \times 10^6$  CAR-positive viable T cells per kg body weight (Wang 2020); maximum dose:  $2 \times 10^8$  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: contraindicated, inadequate response or significant adverse effects to one of the therapies below:
  - a. 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 autoleucel IV).
  - a. Infuse two to four days after completion of chemotherapy (with fludarabine and cyclophosphamide).
  - b. Target dose:  $2 \times 10^6$  CAR-positive viable T cells per kg body weight (Wang 2020); maximum dose:  $2 \times 10^8$  CAR-positive viable T cells.

VI. Abecma intravenous (Idecabtagene Vicleucel IV).

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 know central nervous system involvement.
3. Other therapies:
- a. Immunomodulatory agent (e.g., thalidomide, pomlidomide, 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 Vicleucel IV): Target dose: 300 to 460 × 10<sup>6</sup> CAR-positive viable T-cells. Delay iclecabtagene vicleucel infusion up to seven days for unresolved serious adverse events.

**4.0 Codes:**

<b>AFFECTED CODES</b>				
<b>Code</b>	<b>Brand Name</b>	<b>Generic Name</b>	<b>Billing Units (1 unit)</b>	<b>Prior Approval</b>
Q2042	Kymriah	tisagenlecleucel	up t 600 million CAR+ t cells	Y
Q2041	Yescarta	axicabta-gene ciloleuce	Up to 200 million CAR+ t cells	Y
C9076	Breyanzi	Lisocabtagene maraeucel	NA	Y
NA	Abecma	Idecabtagene Vicleuce		Y
NA	Tecartus	brexucabtagene autoleucel		Y

**5.0 References, Citations, Resources & Associated Documents:**

1. Kymriah [package insert] East Hanover, NJ Novartis Pharmaceuticals Corp, October 2020.
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 November 2021.

**6.0 Appendices:**

See pages 8-10.

**7.0 Revision History:**

Original Effective Date: 06/27/2018

Next Review Date: 11/10/2022

<b>Revision Date</b>	<b>Reason for Revision</b>
9/19	Moved to new format; replaced abbreviations, corrected table

Revision Date	Reason for Revision
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

Appendix I: Patient Safety and Monitoring

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



Drug	Adverse Reactions	Monitoring	REMS
Breyanzi intravenous Lisocabtagene maraleucel IV	<ul style="list-style-type: none"> <li>• Cardiovascular: edema (21%), hypertension (14%), hypotension (26%), tachycardia (25%)</li> <li>• Dermatological: skin rash (13%)</li> <li>• Endocrine/Metabolism: hypophosphatemia (grades 3 to 4 - 13%)</li> <li>• Gastrointestinal: abdominal pain (21%), constipation (23%), decreased appetite (28%), diarrhea (26%), nausea (33%), vomiting (21%)</li> <li>• Hematology/Oncology: anemia (grades 3/4: 23%), hyperfibrinogenemia (grades 3/4: 15%), hypogammaglobinemia (32%), neutropenia (grades 3/4: 76%), thrombocytopenia (grades 3/4: 39%)</li> <li>• Hypersensitivity: cytokine release syndrome (46%)</li> <li>• Immunologic: antibody development (11%)</li> <li>• Infection: bacterial infection (13%), infection (29%)</li> <li>• Nervous System: chills (12%), dizziness (24%), encephalopathy (29%), fatigue (48%), headache (30%), insomnia (14%), neurological signs and symptoms (35%), peripheral neuropathy (11%)</li> <li>• Neuromuscular &amp; Skeletal: musculoskeletal pain (37%)</li> <li>• Renal: renal failure syndrome (11%)</li> <li>• Respiratory: cough (23%), dyspnea (16%), upper respiratory tract infection (13%)</li> <li>• Miscellaneous: fever (16%)</li> </ul>		<a href="https://www.BreyanziREMS.com">https://www.BreyanziREMS.com</a>
Abecma Idecabtagene Vicleucel	<ul style="list-style-type: none"> <li>• Cardiovascular: edema (25%), hypertension (11%), hypotension (17%), tachycardia (19%)</li> <li>• Dermatologic: skin rash (14%), xeroderma (11%)</li> <li>• Endocrine &amp; Metabolic: hypophosphatemia (grades 3/4: 45%), weight loss (13%)</li> <li>• Gastrointestinal: constipation (16%), decreased appetite (22%), diarrhea (35%), nausea (29%), vomiting (15%)</li> <li>• Hematologic &amp; Oncologic (grades 3 or 4): anemia (63%), febrile neutropenia (16%), hypogammaglobinemia (21% to 41%; leukopenia (96%), lymphocytopenia (92%), neutropenia (96%), thrombocytopenia (63%)</li> <li>• Hypersensitivity: cytokine release syndrome (85%)</li> <li>• Immunologic: antibody development (47%)</li> <li>• Infection: bacterial infection (15%), infection (51% to 70%; serious infection: 19%), viral infection (27%)</li> <li>• 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%0)</li> <li>• Neuromuscular &amp; Skeletal: musculoskeletal pain (45%)</li> <li>• Respiratory: cough (23%), dyspnea (13%), pneumonia (17%), upper respiratory tract infection (34%)</li> <li>• Miscellaneous: fever (25%), physical health deterioration (11%)</li> </ul>		<a href="https://www.abecmarems.com/">https://www.abecmarems.com/</a>

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

\*Grade 3 or 4