



MASSACHUSETTS

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## Medical Policy

# Chimeric Antigen Receptor Therapy for Multiple Myeloma

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### Policy Number: 942

BCBSA Reference Number: 8.01.66 (For Plan internal use only)

### Related Policies

- Adoptive Immunotherapy #455
- CAR T-Cell Therapy Services for Multiple Myeloma Prior Authorization Request Form #943
- Cellular Immunotherapy for Prostate Cancer #268
- Chimeric Antigen Receptor Therapy for Leukemia and Lymphoma #066

### Policy

#### Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

#### **Prior Authorization Request Form: Chimeric Antigen Receptor Therapy for Multiple Myeloma**

This form **must** be completed and faxed to: Medical and Surgical: 888-973-0726; Medicare Advantage: 1-800-447-2994.

[CAR T-Cell Therapy Services for Multiple Myeloma \(Idecabtagene Vicleucel\) Prior Authorization Request Form #943](#)

#### **Idecabtagene Vicleucel (ABECMA): Multiple Myeloma**

Idecabtagene vicleucel may be considered **MEDICALLY NECESSARY** for patients with multiple myeloma if they meet **criteria 1 through 6**:

1. Are adults (age  $\geq 18$ ) at the time of infusion
2. Have a documented diagnosis of multiple myeloma
3. Have relapsed\* or refractory disease\* after 4 or more prior lines of therapy\*, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody
4. Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist
5. Does not have active infection(s) or inflammatory disorders
6. Have not received prior FDA approved, BCMA-directed, chimeric antigen receptor T therapy.

#### **Ciltacabtagene autoleucel (Carvykti): Multiple Myeloma**

Ciltacabtagene autoleucel may be considered **MEDICALLY NECESSARY** for patients with multiple myeloma if they meet **criteria 1 through 6**:

7. Are adults (age ≥18) at the time of infusion
8. Have a documented diagnosis of multiple myeloma
9. Have relapsed\* or refractory disease\* after 4 or more prior lines of therapy\*, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody
10. Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist
11. Does not have active infection(s) or inflammatory disorders
12. Have not received prior FDA approved, BCMA-directed, chimeric antigen receptor T therapy.

**\*Relapsed Multiple Myeloma**

Relapse requires **1 or more** of the following direct indicators of increasing disease and/or end organ dysfunction that are considered related to the underlying plasma cell proliferative disorder.

1. Development of new soft tissue plasmacytomas or bone lesions
2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion
3. Hypercalcemia (>11.5 mg/dL) [2.875 mmol/L]
4. Decrease in hemoglobin of >2 g/dL [1.25 mmol/L] or to <10 g/dL
5. Rise in serum creatinine by 2 mg/dL or more [177 μmol/L or more]
6. Hyperviscosity.

Source: 2016 International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma

**\*Refractory Multiple Myeloma**

Refractory multiple myeloma is defined as documented progressive disease during or within 60 days (measured from the last dose) of completing treatment with the last anti-myeloma drug regimen.

Source: The Protocol of the pivotal KarMMa study

Progression is defined as an increase of ≥25% from the lowest response value in **any 1 or more** of the following:

- Serum M-component (the absolute increase must be ≥0.5 g/dL) and/or
- Urine M-component (the absolute increase must be ≥200 mg/24 hour) and/or
- Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved free light chains levels (the absolute increase must be >10 mg/dL)
- Only in subjects without measurable serum and urine M-protein levels and without measurable disease by free light chains levels: bone marrow plasma cell percentage (the absolute percentage must be ≥10%)
- Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
- Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder.

Source: 2016 International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma

**\*Prior Lines of Therapies for Multiple Myeloma**

Three common classes of antimyeloma medications include anti-CD38 monoclonal antibodies (such as daratumumab or isatuximab), immunomodulatory drugs (such as thalidomide, lenalidomide, or pomalidomide) and proteasome inhibitors (such as bortezomib, carfilzomib, or ixazomib).

All CAR-T therapies are considered **INVESTIGATIONAL** for all other indications.

**Prior Authorization Information**

**Inpatient**

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

**Outpatient**

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is <b>required</b> .*
Commercial PPO and Indemnity	Prior authorization is <b>required</b> .*

**\*Prior Authorization Request Form: Chimeric Antigen Receptor Therapy for Multiple Myeloma**  
This form must be completed and faxed to: Medical and Surgical: 888-973-0726; Medicare Advantage: 1-800-447-2994.  
[CAR T-Cell Therapy Services for Multiple Myeloma Prior Authorization Request Form #943](#)

## CPT Codes / HCPCS Codes / ICD Codes

*Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.*

*Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.*

*The following codes are included below for informational purposes only; this is not an all-inclusive list.*

The above **medical necessity criteria MUST** be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

### HCPCS Codes

HCPCS codes:	Code Description
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs
J3590	Unclassified biologics
J9999	Not otherwise classified, antineoplastic drugs
Q2055	Idecabtagene vicleucel, up to 460 million autologous b-cell maturation antigen (bcma) directed car-positive t cells, including leukapheresis and dose preparation procedures, per therapeutic dose
Q2056	Ciltacabtagene autoleucel, up to 100 million autologous b-cell maturation antigen (bcma) directed car-positive t cells, including leukapheresis and dose preparation procedures, per therapeutic dose

### ICD-10 Procedure Codes

ICD-10-PCS procedure codes:	Code Description
XW033C3	Introduction of Engineered Autologous Chimeric Antigen Receptor T-cell Immunotherapy into Peripheral Vein, Percutaneous Approach, New Technology Group 3
XW043C3	Introduction of Engineered Autologous Chimeric Antigen Receptor T-cell Immunotherapy into Central Vein, Percutaneous Approach, New Technology Group 3

## Description

### Relapsed/Refractory Multiple Myeloma

Multiple myeloma is a hematologic malignancy characterized by the abnormal growth of plasma cells with production of abnormal proteins instead of typical antibodies. Plasma cell proliferation in the marrow causes bone pain and fractures due to lytic lesions and displaces other marrow cellular elements. The majority of patients with myeloma present with symptoms related to organ involvement, including

hypercalcemia, renal insufficiency, anemia, and bone lesions (known as calcium, renal failure, anemia, and bone lesions [CRAB] symptoms).<sup>1</sup>

Multiple myeloma is a relatively rare cancer with an annual incidence of approximately 7 in 100,000 Americans. It is estimated that 32,270 new cases of multiple myeloma were diagnosed in 2020 and 150,000 Americans are currently living with the disease.<sup>2</sup> The American Cancer Society estimated that there will be approximately 34,920 new cases of multiple myeloma with 12,410 deaths in the United States in 2021.<sup>3</sup>

Multiple myeloma is primarily a disease of older adults, with a median age at diagnosis of 69. African-Americans appear to be at approximately twice the risk of white Americans, while Asian-Americans appear to be at lower risk.<sup>2</sup> The risk for developing multiple myeloma is unusually high in individuals with a history of monoclonal gammopathy of undetermined significance, a benign presence of abnormal monoclonal proteins in the blood. Such individuals are likely to develop multiple myeloma or a related malignancy at a rate of 1% per year.<sup>4</sup>

### **Diagnosis**

Relapsed or refractory multiple myeloma is commonly identified through routine monitoring with laboratory studies using the standard 2016 International Myeloma Working Group response criteria for categorizing progression and relapse.<sup>5</sup> Progression is usually identified by a rise in monoclonal (M) protein in the serum or urine or in the serum free light chain ratio. Not all patients with progression on laboratory testing need immediate treatment. Therapy is indicated if there is a clinical relapse, extramedullary disease, or a rapid rise in paraproteins.

### **Current Treatment**

The majority of patients with multiple myeloma respond to initial therapies that consist of combination treatments and autologous stem cell transplant. However, conventional therapy is not curative and most of these patients will ultimately progress. A small proportion of patients do not respond to initial treatment (i.e., refractory disease).

There is no single standard treatment for patients with relapsed/refractory multiple myeloma and multiple treatment options are used. Most patients experience serial relapse and are treated with the majority of available agents at some point during their disease course. The main pharmacological medications used are monoclonal antibodies (daratumumab, elotuzumab, isatuximab), proteasome inhibitors (bortezomib, carfilzomib, ixazomib), immunomodulatory drugs (lenalidomide, pomalidomide, thalidomide), alkylators, anthracyclines, panobinostat, selinexor, and corticosteroids. A preferred order for their use has not been established. The choice of therapy at each relapse is informed by prior therapies used, response to these treatments, comorbidities, risk stratification, and the location of disease (e.g., extramedullary disease). Three-drug regimens are preferred over 2-drug regimens. However, 2-drug regimens are acceptable alternatives for frail patients who may not be able to tolerate 3-drug regimens. According to the most recent NCCN clinical practice guideline (version 5, 2021), the triplet regimen including dexamethasone combined with a proteasome inhibitor, an immunomodulatory agent, or an anti-CD38 monoclonal antibody should be used as a primary standard therapy for multiple myeloma (category 2A recommendation).<sup>6</sup>

Patients with myeloma who have been treated with the 3 main backbones of interventional therapy (proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies) have poor outcomes to subsequent treatment. Patients with heavily pretreated multiple myeloma that are daratumumab refractory have an expected median overall survival ranging from 6.6 to 9.3 months. Reported median progression-free survival for this population is 2.3 to 3.4 months.<sup>7,8</sup> In the observational MAMMOTH study, among participants with triple-class refractory multiple myeloma on current therapies, the overall response rate was 31% with a median progression-free survival of 3.4 months.<sup>8</sup> Currently, belantamab mafodotin is the only FDA approved single agent treatment for patients who have received at least 4 prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. Belantamab is an anti-B-cell maturation antigen (BCMA) humanized immunoglobulin G (IgG) antibody conjugated to an antineoplastic agent, monomethyl auristatin. This

indication received an accelerated approval based on response rate and continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. An overall response rate in the pivotal DREAMM-2 trial was achieved in 30 of 97 patients studied (31%, 95% confidence interval [CI]: 21 to 43%). The median time to first response was 1.4 months (95% CI: 1.0 to 1.6) and 73% of responders had a duration of response  $\geq$ 6 months.<sup>9</sup>

A summary of side-by-side comparisons of pivotal studies of 3 new treatments targeting the BCMA pathway for heavily pre-treated patients with relapsed refractory multiple myeloma patients who have cycled through numerous previous lines of therapy is provided in Table 1.

**Table 1. Summary of Treatments Targeting BCMA Pathway for Relapsed Refractory Multiple Myeloma**

	Idecabtagene vicleuce <sup>10,11,12</sup>	Ciltacabtagene autoleuce <sup>13</sup>	Belantamab mafodotin <sup>9</sup>
FDA status	Approved March 26, 2021	Approved February 28 <sup>th</sup> 2022	FDA approved August 5, 2020
Proposed/Approved Indication	Treatment of adult individuals with relapsed and/or refractory multiple myeloma who have received at least 3 prior therapies.	Treatment of adult individuals with relapsed and/or refractory multiple myeloma who have received at least 3 prior therapies.	Treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent
Limitation of use	Black box warning due to the risk of cytokine release syndrome, neurologic toxicity, hemophagocytic lymphohistiocytosis/macrophage activation syndrome, and prolonged cytopenia	Black box warning due to the risk of cytokine release syndrome, neurologic toxicity, hemophagocytic lymphohistiocytosis/macrophage activation syndrome, and prolonged cytopenia	Black box warning as 30% of participants in the trials experienced a severe decline in vision, with grade 3 decline in BCVA
Pivotal Trials	KarMMa (NCT03361748)	CARTITUDE (NCT03548207)	DREAMM-2 (NCT03525678)
Design	Single-arm, open-label	Single-arm, open-label	Single-arm, open-label
Key eligibility criteria	Received at least 2 cycles of $\geq$ 3 prior treatment regimens (incl. PI, IMiD, anti-CD38 antibody) and refractory to the last regimen	Received $\geq$ 3 prior treatment regimens (incl. PI, IMiD, anti-CD38 antibody) or are double refractory to a PI and IMiD	Received $\geq$ 3 previous lines of treatments

Population	Mostly triple-class refractory	Mostly triple-class refractory	Quad- and penta-refractory
N	128	126	97 (for 2.5 mg/kg arm only)
<b>Follow-up Duration</b>	13.3 months	12.4 months	13 months
<b>Efficacy %</b>			
OR (as treated) OR (ITT)	72% 63%	97% 75%	- 32%
<b>Median PFS or OS</b>	As-treated PFS = 8.9 months As treated KM estimated OS = 19.4 months	As-treated PFS >12.4 months	ITT OS = 13.8 months
<b>Toxicity</b>	51% CRS Grade 2+	44% CRS Grade 2+ 6% Treatment-related deaths	30% Severe decline in vision (BCVA scale Grade 3+)

## Summary

Multiple myeloma is a hematologic malignancy characterized by abnormal growth of plasma cells with production of abnormal proteins instead of typical antibodies. Plasma cell proliferation in the marrow causes bone pain and fractures due to lytic lesions and displaces other marrow cellular elements. An increase in total or monoclonal proteins can have direct toxic effects on the kidney, resulting in worsening renal function, hypercalcemia, and anemia. Treatment of multiple myeloma includes immunomodulatory agents (thalidomide, lenalidomide, or pomalidomide), proteasome inhibitors (bortezomib, carfilzomib, or ixazomib) and anti-CD38 monoclonal antibodies (daratumumab or isatuximab). While multiple combinations of these agents can lead to remission, most patients eventually relapse. Idecabtagene vicleucel is a B-cell maturation antigen (BCMA) targeting chimeric antigen receptor (CAR) T-cell therapy for the treatment of individuals with relapsed and/or refractory multiple myeloma who have received at least 4 prior therapies.

## Summary of Evidence

For individuals who are adults with relapsed and/or refractory multiple myeloma and have received 4 or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody, the evidence includes 1 single-arm prospective trial. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The KarMMa study was a Phase 2, multicenter, open label study that enrolled adult patients with relapsed or refractory multiple myeloma who received at least 3 different prior lines of therapy including proteasome inhibitors, immunomodulatory agents, and anti-CD38 monoclonal antibodies. A Food and Drug Administration analysis included data from 100 patients who received idecabtagene vicleucel in the dose range of  $300 \times 10^6$  and  $450 \times 10^6$ . The primary end point was an overall response (partial response or better). After a median follow-up of 10.7 months, results showed an overall response rate of 72% and stringent complete responses in 28% of patients. The median time to response was 30 days, and the median duration of response was 11 months, increasing to 19 months for patients who achieved stringent complete responses. Minimal residual disease-negative status ( $<10^{-5}$  nucleated cells) was achieved in 21% of all treated patients and 75% of all patients with a complete response or stringent complete response. In the absence of a randomized controlled trial, it is difficult to draw comparisons with currently available salvage treatment. Historically, in patients with relapsed/refractory multiple myeloma who have disease progression despite receiving the 3 main classes of myeloma therapy, outcomes are poor. Complete responses are infrequent with reported median progression-free survival ranging from 3 to 4 months, and a median overall survival of 8 to 9 months. With idecabtagene vicleucel, any grade cytokine release syndrome occurred in 85% of patients, and grade  $\geq 3$  cytokine release syndrome occurred in 9% of patients. Neurotoxicity occurred in 28% of patients, reaching grade  $\geq 3$  severity in 4% of



patients. Notable limitations of the KarMMa study included lack of an intention-to-treat analysis and a relatively short follow-up period to assess safety and efficacy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are adults with relapsed and/or refractory multiple myeloma and have received 4 or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody, the evidence includes 1 single-arm prospective trial. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The CARTITUDE 1 study was a Phase 2, multicenter, open label study that enrolled adult patients with relapsed or refractory multiple myeloma who received at least 3 different prior lines of therapy including proteasome inhibitors, immunomodulatory agents, and anti-CD38 monoclonal antibodies. A Food and Drug Administration analysis included data from 97 patients who received ciltacabtagene autoleucl in the dose range of 0.5-1.0x10<sup>6</sup> and 1 x 10<sup>8</sup>. The primary end point was an overall response (partial response or better). After a median follow-up of 18 months, results showed an overall response rate of 97% and stringent complete responses in 78% of patients. The median time to response was 30 days, and the median duration of response was 18 months, increasing to 21.8 months for patients who achieved stringent complete responses. In the absence of a randomized controlled trial, it is difficult to draw comparisons with currently available salvage treatment. Historically, in patients with relapsed/refractory multiple myeloma who have disease progression despite receiving the 3 main classes of myeloma therapy, outcomes are poor. Complete responses are infrequent with reported median progression-free survival ranging from 3 to 4 months, and a median overall survival of 8 to 9 months. With ciltacabtagene autoleucl, any grade cytokine release syndrome occurred in 95% of patients. Neurotoxicity occurred in 26% of patients. Notable limitations of the CARTITUDE 1 study included lack of an intention-to-treat analysis and a relatively short follow-up period to assess safety and efficacy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

## Policy History

Date	Action
10/2022	New medically necessary indications added for Ciltacabtagene autoleucl. FDA approved February 28 <sup>th</sup> 2022. Clarified coding information. 10/1/2022.
7/2022	Clarified coding information.
1/2022	Clarified coding information.
10/2021	Clarified coding information.
6/2021	New medical policy describing medically necessary indications. Effective 6/4/2021.

## Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

[Medical Policy Terms of Use](#)

[Managed Care Guidelines](#)

[Indemnity/PPO Guidelines](#)

[Clinical Exception Process](#)

[Medical Technology Assessment Guidelines](#)

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