Abecma (Idecabtagene Vicleucel)*

Medical Policy #: 08.01.35
Original Effective Date: April 2021
Reviewed: April 2022
Revised: April 2022

NOTICE: This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations, or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

This Medical Policy document describes the status of medical technology at the time the document was developed. Since that time, new technology may have emerged, or new medical literature may have been published. This Medical Policy will be reviewed regularly and be updated as scientific and medical literature becomes available; therefore, policies are subject to change without notice.

DESCRIPTION

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. 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 (Abecma) 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.

The American Cancer Society estimates for 2022 that 34,470 new cases will be diagnosed, and 12,640 deaths are expected to occur.

Relapsed/Refractory Multiple Myeloma
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. 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, 2022), 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).

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. 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. 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 ≥6 months.

Clinical Context and Therapy Purpose
The purpose of the intervention is to provide a treatment option that is an alternative to or an improvement on existing therapies for patients with relapsed and/or refractory multiple myeloma who have received 4 or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

Populations
The relevant population of interest is individuals with relapsed and/or refractory multiple myeloma who have received 4 or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

Interventions
The therapy being considered is idecabtagene vicleucel (Abecma), a B-cell maturation antigen (BCMA) chimeric antigen receptor (CAR) T-cell therapy. Manufacturing of idecabtagene vicleucel (Abecma) involves leukapheresis for harvesting T lymphocytes, modification of lymphocytes with a lentiviral vector containing an anti-BCMA antibody, and expansion of modified CAR-T cells. The final idecabtagene vicleucel (Abecma) therapy is designed to recognize and bind to BCMA on the surface of multiple myeloma cells leading to apoptosis. Prior to the infusion, patients receive lymphodepletion therapy that includes fludarabine and cyclophosphamide.

Comparators
The following practice is currently being used to treat relapsed/refractory multiple myeloma. 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.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, quality of life, treatment-related mortality, and treatment-related morbidity.

Historically, overall survival has been the standard endpoint for demonstrating clinical benefit for phase III RCTs in oncology. However, use of overall survival as the primary endpoint typically requires large sample sizes and prolonged follow-up. Further, use of multiple subsequent therapies in multiple myeloma after relapse can confound the interpretation of the overall survival results. Most recent FDA approvals for multiple myeloma have used time to progression or progression free survival as a primary endpoint. Cartier et. al. (2015) published the findings of a meta-analysis of 21 myeloma RCTs (14 first-line, 4 maintenances, and 3 relapsed/ refractory) using trial-level data and reported a moderate to-strong positive correlation between hazard ratios for treatment effects for progression free survival and overall survival and advocated that patient-level data be used to validate these findings.

The 2016 International Myeloma Working Group response criteria is the standard response criteria used for multiple myeloma and are summarized in the below table:

Response Category	**Description**
Stringent complete response	Complete response as defined below plus normal free light chain ratio[a] and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)[b].
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates.
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 hours. In patients in whom the only measurable disease is by serum free light chain levels: a >90% decrease in the difference between involved and uninvolved free light chain levels.

Partial response	≥50% reduction of serum M-protein plus reduction in 24-hour urinary M-protein by ≥90% or to <200 mg per 24 hours. If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved free light chain levels is required in place of the M-protein criteria. If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD)[c] of soft tissue plasmacytomas is also required.
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50 to 89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD)[c] of soft tissue plasmacytomas is also required.
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease.
Progressive Disease[d]	Increase of ≥25% from lowest response value in any 1 or more of the following: • Serum M-component (the absolute increase must be ≥0.5 g/dL)[e] 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 FLC 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 FLC 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
Relapse	Clinical 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.[d] • Development of new soft tissue plasmacytomas or bone lesions • 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 • Hypercalcemia (>11.5 mg/dL) [2.875 mmol/L] • Decrease in hemoglobin of >2 g/dL [1.25 mmol/L] or to <10 g/dL • Rise in serum creatinine by 2 mg/dL or more [177 μmol/L or more] • Hyperviscosity

CR: complete response; FLC: free light chains; IMWG: International Myeloma Working Group; SPD: sum of the products of the maximal perpendicular diameters of measured lesions.

[a] All recommendations regarding clinical uses relating to serum free light chain levels or free light chain ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, UK).
[b] Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.
[c] Plasmacytoma measurements should be taken from the computed tomography portion of the positron emission tomography/computed tomography, or magnetic resonance imaging scans, or dedicated computed tomography scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD.
[d] All response categories require 2 consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy. In the IMWG criteria, CR subjects must also meet the criteria for progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression-free survival. The definitions of relapse, clinical relapse, and relapse from CR are not to be used in calculation of time to progression or progression-free survival.
[e] For progressive disease, serum M-component increases of ≥1 gm/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.

Review of Evidence

Single Arm Trials
The efficacy of Abecma (idecabtagene vicleucel) (also known as ide-cel) was evaluated in KarMMa (NCT03361748), an open-label, single-arm, multicenter study in adult patients with relapsed and refractory multiple myeloma who had received at least 3 prior lines of antimyeloma therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. The study included patients with ECOG performance status of 0 or 1. The study excluded patients with a creatinine clearance of less than or equal to 45 mL/minute, alanine aminotransferase >2.5 times upper limit of normal and left ventricular ejection fraction <45%. Patients were also excluded if absolute neutrophil count <1000 cells/mm3 and platelet count <50,000/mm3. Patients had measurable disease by International Myeloma Working Group (IMWG) 2016 criteria at enrollment. Bridging therapy with alkylating agents, corticosteroids, immunomodulatory agents, proteasome inhibitors, and/or anti-CD38 monoclonal antibodies to which patients were previously exposed was permitted for disease control between apheresis and until 14 days before the start of lymphodepleting chemotherapy. Of 140 patients enrolled, 128 received Abecma (idecabtagene vicleucel). At a median follow-up of 13.3 months, 94 of 128 patients (73%) had a response, and 42 of 128 (33%) had a complete response or better. Minimal residual disease (MRD) negative status ($<10^5$ nucleated cells) was confirmed in 33 patients, representing 26% of all 128 patients who were treated and 79% of the 42 patients who had a complete response or better. The median progression-free survival was 8.8 months (95% confidence interval, 5.6 to 11.6).

Common toxic effects among the 128 treated patients included neutropenia in 117 patients (91%), anemia in 89 (70%), and thrombocytopenia in 81 (63%). Cytokine release syndrome was reported in 107 patients (84%), including 7 (5%) who had events of grade 3 or higher. Neurotoxic effects developed in 23 patients (18%) and were of grade 3 in 4 patients (3%); no neurotoxic effects higher than grade 3 occurred. Cellular kinetic analysis confirmed CAR- T cells in 29 of 49 patients (59%) at 6 months and 4 of 11 patients (36%) at 12 months after infusion. Results of the KarMMa study support Abecma (idecabtagene vicleucel) induced responses in a majority of heavily pretreated patients with refractory and relapsed myeloma; MRD negative status was achieved in 26% of treated patients.

Section Summary
The evidence for use of idecabtagene vicleucel (Abecma) for relapsed and/or refractory multiple myeloma in adults who have received 4 or more prior lines of therapy includes results from the single arm, phase II, KarMMa trial involving 127 patients with relapsed/refractory myeloma, 100 of whom were evaluated for response. The 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. 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 (Abecma), any grade cytokine release syndrome occurred in 85% of patients, and grade ≥3 cytokine release syndrome occurred in 9% of patients. Neurotoxicity occurred in 28% of patients, reaching grade ≥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.

Summary of Evidence
Abecma (idecabtagene vicleucel) is a B-cell maturation antigen (BCMA) directed genetically modified autologous T cell immunotherapy. The Food and Drug Administration (FDA) approved idecabtagene vicleucel (Abecma), (Bristol Myers Squibb) for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. This is the first FDA-approved cell-based gene therapy for multiple myeloma. The efficacy of Abecma (idecabtagene vicleucel) was evaluated in KarMMa (NCT03361748), an open-label, single-arm, multicenter study in adult patients with relapsed and refractory multiple myeloma who had received at least 3 prior lines of antimyeloma therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. Efficacy was established on the basis of overall response rate (ORR), complete response (CR) rate, and duration of response (DOR), as assessed by the Independent Response committee (IRC) based on the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma. Response durations were longer in

patients who achieved a stringent complete response (CR) as compared to patients with a partial response (PR) or very good partial response (VGPR). Of the 28 patients who achieved a stringent CR, it is estimated that 65% (95% CI: 42%, 81%) had a remission lasting at least 12 months. The median duration of response for VGPR patients (n=25) was 11.1 months (95% CI: 8.7, 11.3) and the median duration of response for PR patients (n=19) was 4.0 months (95% CI: 2.7, 7.2). Results of the KarMMa study support Abecma (idecabtagene vicleucel) induced responses in a majority of heavily pretreated patients with refractory and relapsed myeloma. The NCCN guideline for Multiple Myeloma version 5.2022 idecabtagene vicleucel was added to therapy for previously treated multiple myeloma other recommended regimens and is indicated for patients who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN)
Multiple Myeloma Version 5.2022

Therapies for Patients with Late Relapses (>3 Prior Theraoies)
Indicated for patients who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

- Belantamab mafodotin-blmf
- Idecabtagene vicleucel
- Ciltacabtagene autoleucel

Response Criteria for Multiple Myeloma

- **Clinical Relapse**
  - Clinical relapse requires one or more of the following criteria:
    - Direct indicators of increasing disease and/or end organ dysfunction (calcium elevation, renal failure, anemia, lytic bone lesions [CRAB features]) related to the underlying clonal plasma cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice;
    - Development of new soft tissue plasmacytomas or bone lesions (osteoporotic features do not constitute progression);
    - Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as of 50% (and $\geq$ 1cm) increase as measured serially by the SPD of the measurable lesion;
    - Hypercalcemia (> 11 mg/dL);
    - Decrease in hemoglobin of $\geq$ 2 g/dL not related to therapy or other non-myeloma related conditions;
    - Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma;

- Hyperviscosity related to serum paraprotein.

- **Relapse from complete response (to be used only if the endpoint is disease-free-survival)**
  - Any one or more of the following criteria:
    - Reappearance of serum of urine M-protein by immunofixation or electrophoresis;
    - Development of ≥ 5% clonal plasma cells in the bone marrow;
    - Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion or hypercalcemia)

- **Relapsed from MRD negative (to be used only if the endpoint is disease-free survival)**
  - Any one of more of the following criteria:
    - Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma);
    - Reappearance of serum or urine M-protein by immunofixation or electrophoresis;
    - Development of ≥ 5% clonal plasma cells in the bone marrow;
    - Appearance of any other signs of progression (i.e., new plasmacytoma, lytic bone lesion or hypercalcemia)

- **Progressive disease**
  - Any of the following criteria:
    - Increase of 25% from the lowest confirmed response value in one or more of the following criteria
      - ☐ Serum M-protein (absolute increase must be ≥ 0.5 g/dL);
      - ☐ Serum M-protein increase ≥ 1 g/dL, if lowest M component was ≥ 0.5 g/dL);
      - ☐ Urine M-protein (absolute increase must be ≥ 200 mg/24h);
  - In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL);
  - In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥ 10%);
  - Appearance of new lesion(s), 50% increase from nadir in SPD of > 1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion > 1 cm in short axis;
  - ≥ 50% increase in circulating plasma cells (minimum of 200 cells per uL) if this is the only measure of disease

NCCN Drugs and Biologic Compendium

Idecabtagene Vicleucel

Guideline-Disease	Agent	Brand	Pharmacologic Class	NCCN Recommended Use	FDA Indication
Multiple Myeloma	Idecabtagene Vicleucel	Abecma	BCMA-Directed Chimeric-Antigen Receptor T-Cell (CAR-T) immunotherapy	Therapy for previously treated multiple myeloma for late relapse or progressive disease in patients who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent (2A)	Idacabtagene vicleucel is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapse or refractory multiple myeloma after for our more lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD28 monoclonal antibody

Regulatory Status

On March 26, 2021, the Food and Drug Administration approved idecabtagene vicleucel (Abecma), Bristol Myers Squibb) for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. This is the first FDA-approved cell-based gene therapy for multiple myeloma. Idecabtagene vicleucel is a B-cell maturation antigen (BCMA)-directed genetically modified autologous chimeric antigen receptor (CAR) T-cell therapy. Each dose is customized using a patient's own T-cells, which are collected and genetically modified, and infused back into the patient.

The idecabtagene vicleucel label carries a boxed warning for cytokine release syndrome (CRS), neurologic toxicities, hemophagocytic lymphohistiocytosis/ macrophage activation syndrome, and prolonged cytopenias. The most common side effects of idecabtagene vicleucel include CRS, infections, fatigue, musculoskeletal pain, and hypogammaglobulinemia.

Idecabtagene vicleucel is approved with a risk evaluation and mitigation strategy requiring that healthcare facilities that dispense the therapy must be specially certified to recognize and manage CRS and nervous system toxicities. To evaluate long-term safety, the FDA is requiring the manufacturer to conduct a post-marketing observational study involving patients treated with idecabtagene vicleucel.

The safety and efficacy of Abecma in patients under 18 years of age have not been established.

PRIOR APPROVAL

Prior approval is required.

POLICY

See Related Medical Policies

- 08.01.27 Cellular Immunotherapy for Prostate Cancer – Provenge (Sipuleucel-T)
- 08.01.29 Yescarta (Axicabtagene Ciloleucel)*
- 08.01.30 Kymriah (Tisagenlecleucel)*
- 08.01.33 Tecartus (Brexucabtagene Autoleucel)*
- 08.01.34 Breyanzi (Lisocabtagene Maraleucel)*

Abecma (Idecabtagene Vicleucel) as a one-time, single administration intravenous infusion treatment is considered **medically necessary** when **ALL** of the following criteria are met:

- Individual is 18 years or older; **and**
- Individual has confirmed diagnosis of multiple myeloma by bone marrow evaluation based on medical documentation; **and**
- Individual has relapsed or refractory disease after four or more prior lines of therapy, including the following:
    - An immunomodulatory agent (Thalidomide [Thalomid], Revlimid [Lenalidomide], Pomalidomide [Pomalyst];
    - A proteasome inhibitor (Velcade [bortezomib], Kyprolis [Carfilzomib], Ixazomib [Ninlaro]);
    - An anti-CD38 monoclonal antibody (Daratumumab [Darzalex], Elotuzumab [Empliciti], Isatuximab [Sarclisa]); **and**
- Do not have any of the following:
    - Creatinine clearance $\leq$ 45mL/minute; **or**

- Alanine aminotransferase (SGPT) >2.5 times upper limit of normal; **or**
- Ejection fraction <45%; **or**
- Neutrophil count <1000 cells/mm^3; **or**
- Platelet count <50,000/mm^3; **or**
- Active hepatitis B (HBsAG positive) or hepatitis C virus (anti-HCV positive), if viral load is detectable; a history of hepatitis B or hepatitis C is permitted if the viral load is undetectable per quantitative PCR and/or nucleic acid testing); **or**
- Active infection; **or**
- Active inflammatory disorder; **or**
- Central nervous system (CNS) involvement with myeloma; **or**
- History or presence of CNS disorders such as epilepsy/seizure disorder, paresis, aphasia, stroke, cerebral edema, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or pyschosis; **or**
- History of chimeric antigen receptor therapy (CAR-T) or other genetically modified T-cell therapy; **and**

- The individual will receive Abecma (Idecabtagene Vicleucel) at a treatment center that is certified to administer Abecma (Idecabtagene Vicleucel).

Abecma (Idecabtagene Vicleucel) is considered **investigational** for all other indications, including when the above medical necessity criteria are not met as the safety and efficacy has not yet been established in the peer reviewed medical literature for any other indications and the evidence is insufficient to determine the effects on net health outcomes.

Repeat Treatment
Repeat treatment of Abecma (Idecabtagene Vicleucel) for any indication is considered investigational, as the safety and efficacy beyond one dose has not been studied. The evidence is insufficient to determine the effects on net health outcomes.

Policy Guidelines

Required Documentation
The patient's medical records submitted for review should document the above medical necessity criteria is met and should also include the following:

- Office notes that contain the confirmed diagnosis and clinical features of the diagnosis (including laboratory results confirming the diagnosis), relevant history and physical and prior cancer treatment history.
- Lab work and diagnostic testing within 7 to 14 days of the approval request to determine the individual has adequate organ and bone marrow function and meets the medical necessity criteria above.

Abecma (idecabtagene vicleucel) carries a black box warning for cytokine release syndrome (CRS), neurologic toxicities, hemophagocytic lymphohistiocytosis/ macrophage activation syndrome, and prolonged cytopenias. The most common side

effects of idecabtagene vicleucel include CRS, infections, fatigue, musculoskeletal pain, and hypogammaglobulinemia. It is recommended that severe or life-threatening cytokine release syndrome should be treated with tocilizumab.

Abecma (idecabtagene vicleucel) should not be administered to patients with active infection or inflammatory disorders.

Because of the risk of CRS and neurologic toxicities, Abecma (idecabtagene vicleucel) is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Abecma REMS. The requirement for the REMS components of the Abecma REMS are the following:

- Health care facilities that dispense and administer Abecma must be enrolled and comply with the REMS requirements.
- Certified health care facilities must have onsite, immediate access to tocilizumab, and ensure that a minimum of 2 doses of tocilizumab are available for each patient for administration within 2 hours after Abecma, if needed for treatment of cytokine release syndrome (CRS).
- Certified health care facilities must ensure that health care providers who prescribe, dispense, or administer Abecma are trained about the management of cytokine release syndrome (CRS) and neurologic toxicities.

Refractory Myeloma

- Primary refractory myeloma is defined as disease that is non-responsive; patients who have never received MR or better with any therapy; and double-refractory multiple myeloma (MM) refers to disease refractory to both proteasome inhibitors and immunomodulatory drugs.

Relapsed Myeloma

- Reappearance of signs and symptoms of multiple myeloma (MM) after a period of improvement.

Response Criteria for Multiple Myeloma

- **Clinical Relapse**
  - Clinical relapse requires one or more of the following criteria:
    - Direct indicators of increasing disease and/or end organ dysfunction (calcium elevation, renal failure, anemia, lytic bone lesions [CRAB features]) related to the underlying clonal plasma cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice;
    - Development of new soft tissue plasmacytomas or bone lesions (osteoporotic features do not constitute progression);
    - Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as of 50% (and $\geq$ 1cm) increase as measured serially by the SPD of the measurable lesion;

- Hypercalcemia (> 11 mg/dL);
- Decrease in hemoglobin of ≥ 2 g/dL not related to therapy or other non-myeloma related conditions;
- Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma;
- Hyperviscosity related to serum paraprotein.

- **Relapse from complete response (to be used only if the endpoint is disease-free-survival)**
  - Any one or more of the following criteria:
    - Reappearance of serum of urine M-protein by immunofixation or electrophoresis;
    - Development of ≥ 5% clonal plasma cells in the bone marrow;
    - Appearance of any other sign of progression (i.e. new plasmacytoma, lytic bone lesion or hypercalcemia)

- **Relapsed from MRD negative (to be used only if the endpoint is disease-free survival)**
  - Any one of more of the following criteria:
    - Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma);
    - Reappearance of serum or urine M-protein by immunofixation or electrophoresis;
    - Development of ≥ 5% clonal plasma cells in the bone marrow;
    - Appearance of any other signs of progression (i.e. new plasmacytoma, lytic bone lesion or hypercalcemia)

- **Progressive disease**
  - Any of the following criteria:
    - Increase of 25% from the lowest confirmed response value in one or more of the following criteria
      - ☐ Serum M-protein (absolute increase must be ≥ 0.5 g/dL);
      - ☐ Serum M-protein increase ≥ 1 g/dL, if lowest M component was ≥ 0.5 g/dL);
      - ☐ Urine M-protein (absolute increase must be ≥ 200 mg/24h);
  - In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL);
  - In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥ 10%);

- Appearance of new lesion(s), 50% increase from nadir in SPD of > 1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion > 1 cm in short axis;
- ≥ 50% increase in circulating plasma cells (minimum of 200 cells per uL) if this is the only measure of disease

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 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 (eg, 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
- Revenue Code 0891 Special Process Drugs – FDA Approved Cell Therapy
- Q2055 Idecabtagene vicleucel, up to 460 million autologous b-cell maturation antigen (bcma) directed car-positive cells, including leukapheresis and dose preparation procedures, per therapeutic dose.

SELECTED REFERENCES

- Food and Drug Administration (FDA) Drug approvals. FDA approval idecabtagene-vileucel for multiple myeloma https://www.fda.gov
- Munshi N, Anderson L, Shah M, et.al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. N Engl J Med 2021; 384; 705-716
- National Comprehensive Network (NCCN) Multiple Myeloma Version 5.2022. Also available at https://www.nccn.org
- FDA Labeling Package Insert Abecma (Idecabtagene -Vicleucel)
- KarMMA Clinical Trail NCT03361748
- Mikhael J, Ismaila N, Cheung MC, et al. Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline. J Clin Oncol. May 10 2019; 37(14): 1228-1263. PMID 30932732
- Pick M, Vainstein V, Goldschmidt N, et al. Daratumumab resistance is frequent in advanced-stage multiple myeloma patients irrespective of CD38 expression and is related to dismal prognosis. Eur J Haematol. May 2018; 100(5): 494-501. PMID 29453884

- Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. Leukemia. Sep 2019; 33(9): 2266-2275. PMID 30858549
- Lonial S, Lee HC, Badros A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. Lancet Oncol. Feb 2020; 21(2): 207-221. PMID 31859245
- Janssen Press Release, Dec 5, 2020. Early, Deep, Durable Responses of Ciltacabtagene Autoleucel (cilta-cel) Observed in Phase 1b/2 CARTITUDE-1 Study Show Potential of BCMA CAR-T in Treatment of Heavily Pretreated Patients with Multiple Myeloma. https://www.janssen.com/early-deep-durable-responses-ciltacabtagene-autoleucel-cilta-cel-observed-phase-1b2-cartitude-1
- Holstein SA, Suman VJ, McCarthy PL. Should Overall Survival Remain an Endpoint for Multiple Myeloma Trials? Curr Hematol Malig Rep. Feb 2019; 14(1): 31-38. PMID 30661162

POLICY HISTORY

Date	Reason	Action
April 2022	Annual Review	Policy Revised
April 2021		New Medical Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

*CPT® is a registered trademark of the American Medical Association.