Subject: Chimeric Antigen Receptor T Cell Therapy (CAR T-cell Therapy): Abecma (idecabtagene vicleucel)		Original Effective Date: 6/9/2021
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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

The intent of the policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical studies, nationally recognized authoritative references, and current peer-reviewed scientific literature. Molina Healthcare reserves the right to update this policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available. The information outlined in the MCP includes but is not limited to a review of evidence-based information obtained from the following sources Evaluation of New and Existing Technologies (UM 10). This policy is intended to address coverage criteria that are appropriate for the majority of individuals/members with a particular disease, illness, or condition. Each member's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

RECOMMENDATION

This policy addresses the use of Abecma (idecabtagene vicleucel; ide-cel), an autologous chimeric antigen receptor (CAR) T-cell therapy, for relapsed or refractory multiple myeloma.

Molina Healthcare reserves the right to update this policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available.

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

Multiple myeloma (MM) is characterized by the expansion of malignant plasma cells in the bone marrow, resulting in an overabundance of monoclonal paraprotein (M protein), destruction of bone, and displacement of other hematopoietic cell lines. MM generally remains an incurable disease and most patients will eventually relapse following initial therapies and develop R/R MM. The depth and duration of response decrease with each successive treatment, as well as survival outcomes. MM accounted for approximately 1.8% (32,000) of all new cancer cases in the U.S. in 2020 with an overall 5-year survival rate estimated at 53% (ACS/Cancer Facts & Figures 2021; NCI/SEER 2020).

Relapsed/refractory MM (R/R MM) is defined as a disease which becomes non-responsive or progressive on therapy or within 60 days of the last treatment in patients who had achieved a minimal response or better on prior therapy. The mainstays of current MM treatment include three broad classes of drugs: immunomodulators, proteasome inhibitors, and monoclonal antibodies. However, patients who have tried the referenced drug classes (referred to as 'triple-class exposed') are unlikely to respond to further treatment attempts, have poor survival prospects and tend to demonstrate poor clinical outcomes with very low response rates (20% to 30%), short duration of response (2 to 4 months) (Kumar et al. 2012; Gandhi et al. 2019; Lonial et al. 2020). Most patients treated for R/R MM will continue to relapse and eventually develop disease refractory to immunomodulators, proteasome inhibitors, and monoclonal antibodies (Mikhael, 2020). Disease that is no longer responsive to each of these classes of treatments is referred to as "triple-class refractory" MM. Current approaches to the treatment of triple-class refractory disease are limited and include conventional chemotherapy, salvage autologous stem cell transplantation, and recycling previous regimens, each of which have generally had short-lived efficacy. There is no consensus on standard practice or regimen; a preferred order for conventional therapies has not been established and practice varies widely.

CAR T-cell therapy against MM-associated antigens provides an additional option and promising positive response rates for patients with R/R MM. CAR T-cells are a form of immunotherapy in which immune cells are genetically engineered to target an antigen present on tumor cells so that they seek out those cells specifically; these T-cells then initiate an active and sustained immune response against the target cells (Skrabek, P et al. 2019). BCMA has been identified as a significant CAR target for treatment of MM since it is overexpressed on plasma cells but appears to be minimally expressed on other cells. **Abecma (idecabtagene vicleucel; ide-cel)** is the first cell-based gene therapy approved for MM and is a first-in-class CAR-T cell therapy with BCMA-targeting single-domain antibodies for individuals with MM. As an anti-BCMA CAR T-cell therapy, ide-cel recognizes and binds to BCMA on the malignant plasma cells in MM, leading to the death of cancer cells. The FDA approved indication for Abecma is for the treatment of adult patients with R/R MM after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

FDA INDICATIONS

FDA-approved indication does not alone dictate coverage. Molina Clinical Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.

Multiple myeloma, relapsed or refractory
Treatment of relapsed or refractory multiple myeloma in adults after 4 or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody

Available as: 50mL, 250mL, and 500mL infusion bags containing a frozen suspension of genetically modified autologous T cells in 5% DMSO. A single dose of contains a cell suspension of 300 to 460 x 10^6 CAR-positive T cells in 1 or more infusion bags.

Approved by the FDA: March 26, 2021

- *Orphan Drug and Breakthrough Therapy designations*

Boxed Warning
Cytokine Release Syndrome (CRS), Neurologic Toxicities, Hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), and Prolonged Cytopenia

- CRS, including fatal or life-threatening reactions, occurred in patients following treatment with idecabtagene vicleucel. Do not administer ide-cel to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.
- Neurologic toxicities, which may be severe or life-threatening, occurred following treatment with ide-cel, including concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic events after treatment with ide-cel. Provide supportive care and/or corticosteroids as needed.
- HLH/MAS, including fatal and life-threatening reactions, occurred in patients following treatment with ide-cel. HLH/MAS can occur with CRS or neurologic toxicities.
- Prolonged cytopenia with bleeding and infection, including fatal outcomes following stem cell transplantation for hematopoietic recovery, occurred following treatment with ide-cel.

Risk Evaluation and Mitigation Strategy (REMS): Abecma is available only through the ABECMA REMS due to the serious risks of CRS and neurologic toxicities.

CLASSIFICATION: Antineoplastic Agent, Anti-CD19; Antineoplastic Agent, CAR-T Immunotherapy; CAR-T Cell Immunotherapy; Cellular Immunotherapy, Autologous; Chimeric Antigen Receptor T-Cell Immunotherapy

CENTERS FOR MEDICARE & MEDICAID SERVICES (CMS)

On August 7th, 2019 CMS published a National Coverage Determination (NCD) regarding CAR-T therapy coverage in the Medicare program. According to the NCD, for services performed on or after August 7, 2019, CMS covers autologous treatment for cancer with T-cells expressing at least one chimeric antigen receptor (CAR) when administered at healthcare facilities enrolled in the FDA risk evaluation and mitigation strategies (REMS) and used for a medically accepted indication as defined at Social Security Act section 1861(t)(2) -i.e., is used for either an FDA-approved indication (according to the FDA-approved label for that product), or for other uses when the product has been FDA-approved and the use is supported in one or more CMS-approved compendia. Reference Publication 100-03, National Coverage Determination (NCD) **Manual Section 110.24** for complete coverage criteria. (Rev. 10454, Issued: 11-13-20, Effective: 08-07-19, Implementation: 02-16-21)

NOTE: On 11/2020, a Change Request (CR) was issued to inform of coverage effective for claims with dates of service on or after August 7, 2019 [Link: TN 10454 (Medicare Claims Processing)]

COVERAGE CRITERIA FOR INITIAL AUTHORIZATION

Abecma (idecabtagene vicleucel; ide-cel) may be authorized as one-time treatment course when **ALL** the following criteria are met: [ALL]

1. **Prescriber specialty**

   - ❒ Prescribed by, or in consultation with, an oncologist/hematologist at a certified treatment center

2. **Diagnosis/Indication [ALL]**
   Documentation of ALL of the following criteria are required. May include chart notes from the member's medical records, relevant labs and/or tests, and other relevant clinical information.

   - ❒ Confirmed diagnosis of multiple myeloma by bone marrow evaluation based on medical documentation

   - ❒ Member has measurable disease defined as ONE or more of following. Documentation required [ONE]
     - ❍ Serum monoclonal paraprotein (M-protein) level greater than or equal to 1 g/dL; OR
     - ❍ Urine M-protein level greater than or equal to 200 mg per 24 hours; OR
     - ❍ Serum immunoglobulin free light chain greater than or equal to 10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio

3. **Age/Gender/Other restrictions**

- ❒ 18 years or older at time of infusion

- ❒ Women of child-bearing potential:
  - ❍ Negative serum pregnancy test within the past 30 days
    AND
  - ❍ Prescriber attestation that member has been counseled on the use of effective contraception during treatment

4. **Step/Conservative Therapy/Other condition Requirements**

- ❒ Member has relapsed or refractory disease after FOUR (4) or more prior lines of therapy, including ALL the following: [ALL]
  - ❍ Proteasome inhibitors [e.g., bortezomib (Velcade), carfilzomib (Kyprolis); ixazomib (Ninlaro)]
    AND
  - ❍ Immunomodulatory agents [e.g., lenalidomide (Revlimid), pomalidomide (Pomalyst), thalidomide (Thalomid)]
    AND
  - ❍ An anti-CD38 monoclonal antibody [e.g., daratumumab (Darzalex); elotuzumab (Empliciti), isatuximab (Sarclisa)]

  AND
  Member was refractory to the most recently received therapy. Refractory disease defined as ≤ 25% response to, or progressing during therapy within 60 days after last therapy.

- ❒ Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1[KarMMa pivotal study]

- ❒ Adequate bone marrow, cardiac, pulmonary, and organ function AND deterioration is not expected within four (4) weeks after Abecma intravenous infusion, as determined by the treating oncologist/hematologist

  NOTE: Lab results must be submitted within 14 days of authorization confirming that member has adequate organ and bone marrow function

  NOTE: While not a labeled contraindication, the KarMMa pivotal 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%; and absolute neutrophil count < 1000 cells/mm^3 and platelet count <50,000/mm^3.

- ❒ If member has a history of allogeneic stem cell transplant: Documentation that member has no signs of active graft versus host disease (GVHD)

- ❒ Clinical notes from member's medical records including: all relevant history and physical exams, disease staging, all prior therapies and cancer treatment history, anticipated treatment course applicable, labs and/or tests supporting the diagnosis (lab results must be dated within 14 days of request)

- ❒ Prescriber attestation that member will not receive ANY of the following:
  - ❍ A G-CSF agent within the first 3 weeks after Abecma infusion or until CRS has resolved
    - *Patients may exhibit prolonged cytopenias following lymphodepleting chemotherapy and Abecma infusion. In the KarMMa study, 41% of patients (52/127) experienced prolonged Grade 3 or 4 neutropenia and 49% (62/127) experienced prolonged Grade 3 or 4 thrombocytopenia that had not resolved by Month 1 following Abecma infusion. In 83% (43/52) of patients who recovered from Grade 3 or 4 neutropenia after Month 1, the median time to recovery from Abecma infusion was 1.9 months.*

    AND
  - ❍ Live virus vaccine for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Abecma treatment and until immune recovery following treatment with Abecma

5. Exclusions/*Contraindications

***There are no contraindications listed in the manufacturer's labeling at this time.*

Absence of ALL of the following conditions: [ALL]

- ❒ Active hepatitis B virus (HBsAG positive) or active hepatitis C virus (anti-HCV positive) if viral load is detectable; Human immunodeficiency virus (HIV) positive
  NOTE: A history of hepatitis B or hepatitis C is permitted if the viral load is undetectable per quantitative PCR and/or nucleic acid testing
- ❒ Active, uncontrolled infections (fungal, bacterial, viral, or other uncontrolled infections)
  NOTE: *Uncontrolled or requires IV antimicrobials (antibiotics, antifungals, antiprotozoals, antivirals)
- ❒ Active inflammatory disorder
- ❒ Presence or history of:
  - ❍ Plasma cell leukemia
  - ❍ CNS involvement with myeloma
  - ❍ CNS disorders (i.e. epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis)
- ❒ Prior treatment, or being considered for treatment with:
  - ❍ An allogeneic hematopoietic stem cell transplantation,
  - ❍ CAR-T therapy or other gene therapy; BCMA-targeted therapy; investigational cellular therapy for cancer
  - ❍ Abecma (repeat administration); refer to 'Coverage Exclusions' section of policy

- ❒ History of class III or IV congestive heart failure (CHF) or severe non-ischemic cardiomyopathy, history of stroke, unstable angina, myocardial infarction, or ventricular arrhythmia within the previous 6 months
- ❒ Inadequate organ function
- ❒ Ongoing treatment with chronic immunosuppressants
- ❒ Second malignancies in addition to myeloma if the second malignancy has required therapy in the last 3 years or is not in complete remission
- ❒ Solitary plasmacytomas or non-secretory myeloma without other evidence of measurable disease

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful but are not sufficient documentation unless ALL specific information required by this MCP are included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

1. Recommended Dosage

- ❒ A treatment course consists of lymphodepleting chemotherapy (consists of fludarabine 30 mg/m^2/day and cyclophosphamide 300 mg/m^2/day concurrently for 3 days) followed by idecabtagene vicleucel infusion 2 days after completion of lymphodepleting chemotherapy. Confirm availability of autologous idecabtagene vicleucel prior to initiating lymphodepleting chemotherapy.
    - Premedication (acetaminophen and diphenhydramine) is required prior to idecabtagene vicleucel infusion. Ensure tocilizumab and emergency equipment are available prior to infusion and during recovery period.
- ❒ Abecma (IV infusion only)
    - ❍ For autologous use only, administer 2-7 days after completing lymphodepleting chemotherapy
    - ❍ **300 to 460 × 10^6 CAR-positive viable T-cells IV**

2. Authorization Limit

- ❒ Initial Authorization: ONE (1) single treatment course of Abecma per lifetime
- ❒ Concurrent Authorizations: Authorizations for Abecma will also receive approval of **Actemra (tocilizumab).** Max 8 single dose vials per lifetime **[Actemra (tocilizumab) Policy No: C10265-A]**
    - Actemra (tocilizumab) is indicated for the treatment of CAR T cell-induced severe or life-threatening CRS in patients ≥ 2 years of age. According to the FDA approved labeling for intravenous tocilizumab, the dose should not exceed 800 mg per infusion every 4 weeks for RA or CRS patients [Actemra (tocilizumab); prescribing information, 2020]
- ❒ Reauthorization/Continuation of Treatment Authorization: NOT recommended; will not be authorized
    - *Repeat administration of CAR-T cell is experimental and investigational since the safety and efficacy beyond one treatment has not been studied and is not indicated in the current FDA approval for Abecma. The evidence is insufficient to determine the effects on net health outcomes.*

3. Route of Administration

- ❒ Provider-administered in certified treatment centers enrolled and comply with the REMS requirements
    - Certified healthcare facilities must have on-site, immediate access to tocilizumab.
    - Ensure that a minimum of 2 doses of tocilizumab are available for each patient for infusion within 2 hours after Abecma infusion, if needed for treatment of CRS.
    - Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense, or administer Abecma are trained on the management of CRS and neurologic toxicities.

Reauthorization /Continuation of Therapy

The safety and efficacy of repeat treatment has not been studied and is currently not supported by any compendia nor indicated in the current FDA approved labeling. Requests for reauthorization or beyond one dose is considered not medically necessary and will not be authorized.

Coverage Exclusions

All other uses of Abecma (idecabtagene vicleucel; ide-cel) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy, including but not limited to the following, due to insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcomes. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

- ❒ Prior treatment with any form of CAR T-cell therapy, or repeat administration of Abecma
  - *Repeat administration of CAR-T cell is experimental and investigational since the safety and efficacy beyond one treatment has not been studied and is not indicated in the current FDA approval for Abecma. The evidence is insufficient to determine the effects on net health outcomes.*

- ❒ Pregnancy: Not recommended for women who are pregnant, and pregnancy after Abecma infusion should be discussed with the treating physician
  - *It is not known if Abecma has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia and hypogammaglobulinemia.*

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

Summary of Clinical Evidence

FDA approval for Abecma (idecabtagene vicleucel) was based on data from the pivotal Phase 2 KarMMa study that evaluated its safety and efficacy in adults with R/R MM in North America and Europe (NCT03361748).

- The study met its primary endpoint of overall response rate and key secondary endpoint of complete response rate.
- Of 140 patients enrolled, 128 received Abecma. 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 (<105 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).
- The efficacy evaluable population consists of 100 patients (n=100). Overall, 72 participants (72%) responded to Abecma and achieved a partial or complete response to treatment, including 44 whose tumors partially shrunk and 28 whose tumors disappeared completely (28%).

- 28% of patients who had a complete response or remission (with disappearance of all signs of MM) and this was sustained by 65% of this group for at least 12 months
- Patients whose tumors disappeared completely stayed in remission for a median of 19 months
- For all participants who responded to the treatment, the remission lasted a median of 11 months

KarMMa (Munshi et al., 2021)

- A pivotal, open-label, single-arm, multicenter, multinational, Phase 2 trial of 127 patients with R/R MM who received at least 3 previous regimens including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody. (Munshi et al., 2021)
- The efficacy evaluable population consists of 100 patients (n=100) who received Abecma within the dose range of 300 to 460 x 10^6 CAR-positive T cells. Of these patients, 88% received four or more prior lines of therapy and 85% were triple-class refractory.
- Patient population included adult patients [median age of 61 years (age range 33-78); majority male (59%)] with measurable disease; and adequate organ function.
- All enrolled patients had received at least 3 prior treatment regimens, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody, and were refractory to their last regimen, defined as progression during or within 60 days of their last therapy.
- The primary endpoint was overall response (partial response or better), defined according to IMWG Uniform Response Criteria for Multiple Myeloma.
- Key secondary endpoint is complete response rate. Other efficacy endpoints include time to response, duration of response, progression-free survival, overall survival, minimal residual disease.
- Primary and secondary end points were met.
- The overall response rate for the efficacy evaluable population (n=100) was 72% and 28% of patients achieved a stringent complete response.
- Responses were rapid and durable, with a median time to response of 30 days (range: 15 to 88 days) and median duration of response of 11 months for all responders and 19 months for those who achieved sCR. Of the 28 patients who achieved stringent complete response, an estimated 65% had remission lasting at least 12 months.
- The most common (≥ 20%) types of nonlaboratory adverse reactions included CRS, infections, fatigue, musculoskeletal pain, hypogammaglobulinemia, diarrhea, upper respiratory tract infection, nausea, viral infections, encephalopathy, edema, pyrexia, cough, headache, and decreased appetite.
- Serious adverse reactions occurred in 67% of patients, with the most common (≥5%) being CRS (18%), general physical health deterioration (10%), pneumonia (12%), infections (19%), viral infections (9%), sepsis (7%), and febrile neutropenia (6%). The most common Grade 3 or 4 nonlaboratory adverse reactions were febrile neutropenia (16%) and infections (14%). Fatal adverse reactions occurred in 6% of patients.
- Abecma carries a boxed warning for CRS, neurological toxicities, HLH/MAS, and prolonged cytopenia. Among 127 patients treated with idecabtagene vicleucel:
    - 85% of patients experienced low-grade CRS and 9% of patients had Grade 3 and higher CRS (only 1 patient had Grade 5 CRS)
    - CRS commonly occurred on day 1 and median time to resolve was 5 days

- Neurotoxicity occurred in 28% of patients with 4% of patients having neurotoxicity over Grade 3; median time to neurotoxicity onset was 2 days and the median time to resolution was 5 days
- HLH/MAS (potential complications related to excessive immune activation associated with CAR T cell therapies) occurred in 4% of patients, including two patients: one who developed fatal multiorgan HLH/MAS with CRS and the second patient with fatal bronchopulmonary aspergillosis with HLH/MAS as a contributing factor

Post-Marketing Requirement (PMR) study

A PMR study has been required to further evaluate long-term safety of ide-cel.

A post-marketing, prospective, multi-center, observational study to assess the long-term safety of ide-cel and the risk of secondary malignancies occurring after treatment with idecabtagene vicleucel. The study will include at least 1500 adult patients with R/R MM after four or more prior lines of systemic therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody; the enrolled patients will be followed for 15 years after product administration.

A digital platform, Cell Therapy 360, is provided by the manufacturer (BMS) to support the patient and physician treatment experience. Patients will be able to track production and receive support and other relevant information. The manufacturer will also provide patients with wearable technology to help patients track their temperature in real time.

Ongoing Clinical Trials

Abecma is being evaluated in several clinical trials in the U.S.

- Phase 3 trial includes:
  - Abecma vs standard treatment regimens for patients with R/R MM (KarMMa-3 trial; NCT03651128)
- Phase 1 and 2 trials include:
  - Abecma in patients with R/R MM and in patients with high-risk MM (KarMMa-2 trial; NCT03601078)
  - Abecma in patients with high-risk, newly diagnosed MM (KarMMa-4 trial; NCT04196491)

Comparative Studies

A head-to-head trial and indirect treatment comparison studies evaluating the safety and efficacy of FDA-approved CAR T-cell therapies for R/R MM patients are lacking. Furthermore, there is insufficient data to perform quantitative indirect comparisons (ICER, Evidence Report April 2021).

Roex G et al. (2020) conducted a systematic review and meta-analysis assess the safety and clinical efficacy of BCMA-targeted CAR-T-cell therapies in patients with MM. The assessment included 27 clinical studies pertaining to 23 different BCMA CAR-T-cell therapies in 640 patients. It is noted that high response rates were achieved for all BCMA CAR-T patients evaluable for clinical response and along with high response rates, toxicity was also high (80.3% patients evaluable for safety experienced CRS with 14.1% experiencing CRS of

grade ≥3) with high dose ide-cel and cilta-cel having higher than average rates of CRS overall (96.3% and 89.5%, respectively).

- The response rates for high dose ide-cel and cilta-cel were comparable (ORR 82% and 88%, respectively).
- The median PFS among evaluable patients treated with high-dose ide-cel was 12.1 months and 19.9 months for patients treated with cilta-cel.

This meta-analysis provides evidence that despite toxicities, BCMA CAR-T therapies are considered highly efficacious, even in heavily pretreated MM patients. This meta-analysis provides robust evidence for the high clinical activity of BCMA CAR-T-cell therapies in MM and shows that several patient- and treatment-related factors might contribute to their toxicity and efficacy.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN)

NCCN Guidelines for Multiple Myeloma V.6.2021

Based on the review of the data and FDA approval, idecabtagene vicleucel is included as an option for the treatment of adult patients with R/R MM with a footnote stating "indicated after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody" for this indication." This is designated as a category 2A, 'other recommended regimen.'

National Institute for Health and Care Excellence (NICE)

NICE is developing guidance on ide-cel for the treatment of patients with RRMM who have received at least 3 prior therapies [GID-TA10672]; The expected publication date is to be confirmed.

Institute for Clinical and Economic Review (ICER)

Evidence report has been prepared and published on April 5, 2021. The final evidence report and policy recommendations is expected on May 5, 2021.

ICER has released an evidence report assessing the comparative clinical effectiveness and value of three new treatments targeting the BCMA for heavily pre-treated patients with triple class refractory MM who have cycled through numerous previous lines of therapy. The Abecma (idecabtagene vicleucel), ciltacabtagene autoleucel ('cilta-cel') and Blenrep (belantamab). A systematic review of cilta-cel and Abecma suggests that the evidence is insufficient to determine whether one agent is superior to the other. It was concluded that 'belantamab is promising but inconclusive compared to usual care for patients with triple-, quad- and penta- refractory MM exposed to 4+ prior lines of treatment. The overall response rate and overall survival suggests a possible small net benefit. However, the frequency and severity of visual impairment and lack of demonstrated improvement in health-related quality of life suggests that any net benefits are likely to be modest. The current evidence precludes a substantial benefit; additional data is required to preclude small overall net harm.' The key clinical findings summarized by the report are as follows:

- While the data are limited and toxicities are common, both Abecma and cilta-cel appear to deliver relatively sizeable gains in both progression-free survival and overall survival for triple class refractory MM patients exposed to three or more prior lines of treatment, with higher rates of response and longer survival than treatment with current therapies. Based on this evidence, ICER determined that there is high certainty that both therapies provide at least a small net health benefit compared to usual care, with the

possibility of a substantial benefit ("B+"). **The evidence remains insufficient ("I") to compare ide-cel and cilta-cel to each other.**

- Belantamab appears to be equivalent or slightly superior to current treatments for triple class refractory MM patients exposed to four or more prior lines of treatment. However, visual disturbances and other toxicities are also common with belantamab, requiring dose reduction or discontinuation in some circumstances. ICER rated the current evidence promising but inconclusive ("P/I"), as the balance of potential benefits and risks did not rule out a small possibility of overall net harm.

American Society of Clinical Oncology (ASCO)
ASCO issued a CAR T-Therapy Policy Brief in 2019 supporting coverage of CAR T-cell therapy for all FDA-approved indications.

DEFINITIONS

Chimeric Antigen Receptor T-cells (CAR T-cells): T-cells that have been genetically altered in order to improve the ability of the T-cells to fight cancer. The genetic modification creates a new and special receptor on the surface of the T-cell. This special receptor is called a CAR and there are many CARs on the surface of the T-cell. CAR enhances the ability of the T-cell to recognize and attach to a specific protein, called an antigen, on the surface of a cancer cell. (CMS)

- Previous CAR T-cell approvals include Kymriah (tisagenleleucel) for the treatment of R/R LBCL in adults or R/R B-cell acute lymphoblastic leukemia; Yescarta (axicabtagene ciloleucel) for the treatment of R/R LBCL; Tecartus (brexucabtagene autoleucel) for the treatment of adults with R/R mantle cell lymphoma; and Breyanzi (lisocabtagene maraleucel) for treatment of R/R LBCL. Kymriah, Yescarta and Breyanzi are indicated for R/R LBCL after two or more lines of systemic therapy.

Cytokine release syndrome (CRS): An acute systemic inflammatory response syndrome characterized by fever, with or without multiple organ dysfunction that is associated with CAR-T cell therapy or other forms of immunotherapy. Clinical manifestations include fever, which may be accompanied by fatigue, headache, rash, diarrhea, arthralgia, and myalgia. Milder CRS can progress to a more severe syndrome, which may include hypotension, hypoxia, and uncontrolled systemic inflammatory response with circulatory collapse, vascular leakage, peripheral and/or pulmonary edema, renal failure, cardiac dysfunction, and multiorgan system failure.

Eastern Cooperative Oncology Group Performance Status (ECOG PS)
A scale used to determine the individual's level of functioning; standard criteria for measuring how the disease impacts a patient's daily living abilities

0 Fully active, able to carry on all pre-disease performance without restriction
1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5 Deceased

The scale was developed by the Eastern Cooperative Oncology Group (ECOG), now part of the ECOG-ACRIN Cancer Research Group and published in 1982.

APPENDIX

N/A

CODING INFORMATION

The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is covered or non-covered. coverage is determined by the benefit document. This list of codes may not be all inclusive.

HCPCS	Description
C9399	Unclassified drugs or biologicals (hospital outpatient use only) [Abecma]
J3490	Unclassified drugs [Abecma]
J3590	Unclassified biologics [Abecma]
J9999	Not otherwise classified, antineoplastic drugs
CPT Code	**Description**
0540T	Chimeric antigen receptor T-cell (CAR T) therapy; CAR T cell administration, autologous
ICD-10	**Description**
C90.00	Multiple myeloma not having achieved remission
C90.02	Multiple myeloma in relapse
Z51.12	Encounter for antineoplastic immunotherapy

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Policy History	Approval
Policy Developed IRO Peer Review: Policy was reviewed by practicing physician board certified in Hematology & Medical Oncology, 4/21/2021	MCPC 6/9/2021

**Annual Review and Policy Revisions: All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections were reviewed and revised with the most recent medical literature and available evidence. Coverage criteria for Initial and Continuation of Therapy were revised/updated as appropriate.*