Drug Monograph

Drug Name: **Abecma® (idecabtagene vicleucel) suspension for intravenous infusion**

Drug Class: **Chimeric Antigen Receptor (CAR) T-Cell Immunotherapy**

Prepared For: MO HealthNet

Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Abecma is available as a suspension for intravenous administration in an infusion bag containing 300 to 460 x10^6 CAR-positive T cells.
Manufacturer:	Manufactured by: Celgene Corporation, a Bristol-Myers Squibb Company, Summit, NJ 07901
Summary of Findings:	The efficacy of Abecma was established in an open-label, single-arm multicenter study of 100 patients with relapsed and refractory multiple myeloma, who received at least three prior antimyeloma lines of therapy. Approximately 88% of patients in the study group had received four or more prior lines of antimyeloma lines of therapy. Overall, 72% of patients partially or completely responded to treatment. Of those studied, 28% of patients showed complete response to Abecma with 65% of this group remaining in complete response to treatment for at least 12 months. Of those 28% of patients showing complete response in the KarMMA study, 21% were evaluable for MRD (minimal residual disease) activity defined as less than one myeloma cell per million bone marrow cells. It was found that 100% of those evaluable patients were MRD negative. A negative MRD after treatment suggests that the patient may be less likely to experience relapse of their condition.
Status Recommendation:	☒ Clinical Edit ☐ PA Required ☐ Open Access ☐ PDL
Type of PA Criteria:	☒ Appropriate Indications ☐ Non-Preferred ☐ No PA Required ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Multiple myeloma (MM) is a relatively rare cancer of plasma cells. In the US, it is estimated that the incidence rate of getting MM is 7 per 100,000 with over 32,000 new cases in 2020. Normal plasma cells are found in the bone marrow and play a key role in the immune system. Plasma cells make the antibodies that help the body attack and kill pathogens. When plasma cells make an abnormal protein (antibody) or often referred to as a monoclonal protein (M-protein), the plasma cells become cancerous and grow out of control, developing what is known as multiple myeloma. MM's key features are low blood counts (anemia, thrombocytopenia, and leukopenia), bone and calcium problems resulting in fractures, infections and kidney problems. Relapsed or refractory MM is defined as those who achieved minor response to treatment, relapse and then progress while on salvage therapy, or experience progression of disease within 60 days of their last therapy. Median survival ranges for relapsed and refractory MM is as little as 6 to 9 months and responses to treatment are typically short.

Dosage Form [4]

Abecma is available as a suspension for intravenous administration in an infusion bag containing 300 to 460 $x10^6$ CAR-positive T cells.

Manufacturer [4]

Manufactured by: Celgene Corporation, a Bristol-Myers Squibb Company, Summit, NJ 07901.

Indication(s) [4]

Abecma is indicated 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.

Clinical Efficacy [3,4] (mechanism of action/pharmacology, comparative efficacy)

Abecma is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T-cell immunotherapy in which a patient's T-cells are reprogrammed via transduction with an anti-BCMA02 chimeric antigen receptor (CAR) lentiviral vector. The CAR construct includes an anti-BCMA single chain variable fragment-targeting domain for antigen specificity, a transmembrane domain, a CD3-zeta T-cell activation domain, and a 4-1BB costimulatory domain. CD3-zeta signaling initiates activation and antitumor activity, while 4-1BB (CD137) signaling enhances T-cell expansion. Antigen-specific activation of Abecma results in CAR-positive T-cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells. Abecma is prepared from the patient's T-cells, which are obtained via leukapheresis.

Pharmacokinetics:
Note: Abecma exhibits an initial rapid expansion followed by a bi-exponential decline. Patients who received tocilizumab and/or corticosteroids to manage cytokine release syndrome (CRS) and/or neurologic toxicity experienced higher Abecma expansion levels and higher $AUC_{0\ to\ 28d}$ and C_{max} compared to patients who did not receive tocilizumab or corticosteroids.

Absorption	Median T_{max} occurred 11 days after infusion and can persist in peripheral blood for up to 1 year post-infusion
Metabolism	Not available
Excretion	Not available
Half-life	Not available

Clinical Trials Experience:

STUDY 1 DESIGN (KarMMa, NCT03361748)	Open-label, single-arm, multicenter study (N=100)
INCLUSION CRITERIA	• ≥18 years of age • Must have received at least 3 prior MM treatment regimens. Note: Induction with or without hematopoietic stem cell transplant and with or without maintenance therapy is considered a single regimen • Must have undergone at least 2 consecutive cycles of treatment for each regimen, unless a partial response (PR) was the best response to the regimen • Must have received a proteasome inhibitor, an immunomodulatory agent, and an antiCD38 antibody • Must be refractory to the last treatment regimen • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
EXCLUSION CRITERIA	• Patients with a creatinine clearance of less than or equal to 45 mL/minute, alanine aminotransferase >2.5 times upper limit of normal (ULN) and left ventricular ejection fraction <45% • Absolute neutrophil count <1000 cells/mm^3 and platelet count <50,000/mm^3
TREATMENT REGIMEN	Pre-treatment: Lymphodepleting chemotherapy consisted of cyclophosphamide (300 mg/m^2 IV infusion daily for 3 days) and fludarabine (30 mg/m^2 IV infusion daily for 3 days) starting 5 days prior to the target infusion date of Abecma. Fludarabine was dose reduced for renal insufficiency. Treatment: Abecma dose range of 300 to 460 x 106 CAR-positive T cells. Post-treatment: Patients were hospitalized for 14 days after Abecma infusion to monitor for potential cytokine release syndrome (CRS), hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), and neurotoxicity.
RESULTS	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.

	The median time to first response was 30 days (n=72; range: 15 to 88 days). Patients experienced an ORR of 72% which consists of both a partial or complete response to the treatment (95% CI: 62, 81). Of the 72 overall responders, 28 were classified as complete responders (95% CI: 19, 38), 25 as very good partial responders (95% CI: 17, 35), and 19 partial responders (95% CI: 12, 28). Of those 28% patients with complete response to Abecma in the KarMMA study, 65% of them group remained in complete response to the treatment for at least 12 months (95% CI: 42, 81), and 21 were evaluable for MRD (minimal residual disease) activity which refers to the number of malignant cells present in bone marrow. Of those 21 MRD evaluable patients, 100% were MRD negative. A negative MRD after treatment suggests that the patient may be less likely to experience a relapse of their condition.
SAFETY	Discussed in the Adverse Effects section below.

Contraindications [3,4]

- None

Warnings and Precautions [3,4]

- **Black Boxed Warnings:**
  - **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients follow treatment with Abecma. Do not administer to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab**
  - **Neurologic toxicities, which may be severe or life-threatening. Monitor for neurologic events and provide supportive care and/or corticosteroids as needed.**
  - **Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS), including fatal and life-threatening reactions, occurred in patients following treatment with Abecma**
  - **Prolonged Cytopenia with bleeding and infection, including fatal outcomes following stem cell transplantation for hematopoietic recovery, occurred following treatment with Abecma**
  - **Abecma is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Abecma REMS**
- Hypersensitivity Reactions: monitor during infusion
- Infections: monitor for signs and symptoms and treat appropriately
- Prolonged cytopenias: Patients may exhibit prolonged Grade 3 or higher cytopenias following infusion. Monitor blood counts prior to and after infusion
- Hypogammaglobulinemia: Monitor and consider immunoglobulin replacement therapy
- Secondary Malignancies: in the event secondary malignancy occurs after treatment, contact Bristol-Meyers Squibb at 1-888-805-4555
- Effects on Ability to Drive and Use Machines: Advise patients to refrain from driving or operating heavy or potentially dangerous machines for at least 8 weeks after administration

Adverse Effects [3,4]

Most common Grade 3 or Higher, ≥ 3%	(N=127) %
Febrile neutropenia	16
Fatigue	3.1
General physical health deterioration	10
Cytokine release syndrome	9
Infections-Pathogen unspecified	15
Bacterial infections	3.9
Pneumonia	9
Musculoskeletal pain	3.1
Encephalopathy	6
Hypertension	3.1

Drug Interactions [3,4]

- Drug/Laboratory Test Interactions: HIV and the lentivirus used to make Abecma have limited, short spans of identical genetic material (ribonucleic acid) and therefore some commercial human immunodeficiency virus (HIV) nucleic acid tests may yield false-positive results in patients who have received Abecma.

Dosage and Administration [3,4]

- For autologous use only
- Dosing of ABECMA is based on the number of chimeric antigen receptor (CAR)-positive T cells
- The recommended dose range is 300 to 460 × 10^6 CAR-positive T cells administered via IV infusion in one or more infusion bags
- Abecma is to be administered 2 days after completion of lymphodepleting chemotherapy regimen.
- Premedication: administer acetaminophen (650 mg orally) and diphenhydramine (12.5 mg IV or 25-50 mg orally, or another H_1-antihistamine) approximately 30 to 60 minutes before infusion of Abecma. Avoid use of dexamethasone or other systemic corticosteroids, as they may interfere with the activity of Abecma.
- Prior to thawing the product, confirm that a minimum of 2 doses of Actemra® and emergency equipment are available prior to the infusion and during the recovery period.
- Abecma should be administered within 1 hour of the start of thaw and is stable for 2 hours at room temperature once thawed. If more than one bag is being used, thaw one at a time.

Cost [5]

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ Month
Idecabtagene vicleucel	Abecma®	Celgene Corporation	300-460 x 10^6 cells	$419,500
Lisocabtagene maraleucel	Breyanzi®	Juno Therapeutics, Celgene, Bristol-Myers Squibb	50 to 110 × 10^6 CAR-positive viable T cells	$410,300
Brexucabtagene autoleucel	Tecartus®	Kite Pharma, Gilead	Target dose: 2 × 10^6 chimeric antigen receptor (CAR)-positive viable T cells per kg body weight	$399,900
Tisagenlecleucel-T	Kymriah®	Novartis	Depends on indication; Maximum dose: 0.6 to 6 x 10^8 CAR-positive viable T cells	$373,000
Axicabtagene ciloleucel	Yescarta®	Kite Pharma, Gilead	Target dose: 2 × 10^6 CAR-positive viable T cells per kg body weight	$399,000

** Wholesale Acquisition Cost

Conclusion

Multiple Myeloma (MM) is a relatively rare cancer of plasma cells. Relapsed or refractory MM is defined as those who achieved minor response to treatment, relapse and then progress while on salvage therapy, or experience progression of disease within 60 days of their last therapy. Median survival ranges for relapsed and refractory MM is as little as 6 to 9 months and responses to treatment are typically short and therefore most MM patients require treatment with several different lines of therapy.

Abecma is a B-cell maturation antigen (BCMA)-directed genetically modified chimeric antigen receptor (CAR) T-Cell therapy. Each dose of Abecma is created by collecting the patient's own T-cells, then genetically modifying those to target and kill myeloma cells and infusing them back into the patient. Abecma is indicated 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.

Overall, 72% of patients partially or completely responded to treatment in the KarMMa study. Treatment with Abecma has the potential to cause severe side effects producing the boxed warning for CRS, HLH/MAS, neurologic toxicity, and prolonged cytopenia, all of which can be fatal or life-threatening. Due to the risk of CRS and neurologic toxicities, Abecma was approved with a risk evaluation and mitigation strategy (REMS program). The Abecma REMS program restricts access to the drug to hospitals and healthcare facilities that are enrolled and certified to have met certain safety criteria. The most common Grade 3 or higher adverse reactions seen with the use of Abecma are febrile neutropenia, general health deterioration, and infections.

Recommendation

The MO Healthnet Division recommends adding this drug to the current CAR T-cell clinical edit.

References

1) National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Multiple myeloma. V.3.2018. Accessed at www.nccn.org on July 2, 2021.
2) Palumbo A, Anderson K. Multiple myeloma. *N Engl J Med*. 2011;364(11):1046-1060.
3) Idecabtagene vicleucel: Drug Information. Lexi-Drugs. Wolters Kluwer Clinical Drug Information Inc.
4) Abecma [package insert]. Summit, NJ: Celgene Corporation; 2021.
5) IPD Analytics Rx Strategy: Oncology: Chimeric Antigen Receptor (CAR) T-Cell Therapy. Accessed July 2, 2021.

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