New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Abecma® (idecabtagene vicleucel) [Bristol Myers Squibb]**
Dosage Formulations:	Cell suspension for infusion comprised of chimeric antigen receptor (CAR)-positive T cells in one or more infusion bags. Recommended dose range is 300 to 460 x 10^6 CAR-positive T cells as a one-time infusion.
FDA Approval Date: **FDB File Date:**	FDA: March 26, 2021 FDB: April 4, 2021
Indication:	Treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.
Mechanism of Action:	• Chimeric antigen receptor (CAR) T cell immunotherapy. • Abecma targets B-cell maturation antigen (BCMA), which is expressed on the surface of normal and malignant plasma cells. The CAR construct includes an antiBCMA scFv-targeting domain for antigen specificity, a transmembrane domain, a CD3-zeta T cell activation domain, and a 4-1BB costimulatory domain. Antigen-specific activation of Abecma results in CAR-positive T cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells.

Dose/ Administration:	• Recommended dose range is 300 to 460 x 10^6 CAR-positive T cells administered via IV infusion in one or more infusion bags.
	• Autologous use only – must verify patient identity prior to infusion. Do not remove infusion bags from cassette if the information on the patient-specific cassette label(s) does not match the intended patient.
	• Pretreatment: administer lymphodepleting chemotherapy regimen of cyclophosphamide 300 mg/m^2 IV and fludarabine 30 mg/m^2 IV daily for 3 days. Abecma is to be administered 2 days after completion of lymphodepleting chemotherapy.
	• Delay the infusion of Abecma up to 7 days if a patient has any of the following conditions:
	  ○ Unresolved serious adverse events (especially pulmonary events, cardiac events, or hypotension), including those after preceding chemotherapies.
	  ○ Active infections or inflammatory disorders.
	• Premedication: administer acetaminophen (650 mg orally) and diphenhydramine (12.5 mg IV or 25-50 mg orally, or another H1-antihistamine) approximately 30 to 60 minutes before infusion of Abecma. Avoid use of dexamethasone or other systemic corticosteroids, as they may interfere with activity of Abecma.
	• Confirm infusion time in advance with patient so that Abecma will be available for infusion when the patient is ready. 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 infusion bag has been received to achieve the treatment dose, thaw each infusion bag one at a time. Do not initiate thaw of the next bag until infusion of the previous bag is complete.
	• Ensure at least 2 doses of tocilizumab and emergency equipment are available prior to Abecma infusion and during the recovery period.
	• Monitor patients at least daily for 7 days following Abecma infusion at the certified healthcare facility for signs and symptoms of cytokine release syndrome (CRS) and neurologic toxicities.
	• Instruct patients to remain within proximity of the certified healthcare facility for at least 4 weeks following infusion.
	• Instruct patients to refrain from driving or hazardous activities for at least 8 weeks following infusion.

Disease State Clinical Highlights:

- Multiple myeloma (MM) is a plasma cell malignancy in which monoclonal plasma cells proliferate in bone marrow, resulting in an overabundance of monoclonal paraprotein (M protein), destruction of bone, and displacement of other hematopoietic cell lines.
- MM accounts for 10% of all hematologic cancers. Median age at diagnosis of MM is 69 years. Survival range is 1 to 10 years, with a 5-year relative survival rate of 46.6%.
- The estimated incidence rate of MM in the United States is 7 per 100,000 persons with approximately 32,270 new cases in 2020. With the aging population, the number of cases is expected to increase.

Drug Clinical Highlights:

- CAR-T cell therapy is a type of immunotherapy that involves genetically modifying a patient's own T cells to recognize and attack cancer cells.
- Abecma is the first CAR-T cell therapy approved for adults with RRMM.
- Safety and efficacy was evaluated in an open-label, single-arm, multicenter study (KarMMa; NCT03361748)
  - Included adult patients with RRMM who had received at least 3 prior lines of antimyeloma therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.
  - Of the 135 patient who underwent leukapheresis, 100 were evaluable for efficacy.
    - The median participant age was 62 years (range 33 to 78), 60% of which were male.
    - The median number of prior lines of therapy was 6 (range 3 to 16). 92% of patients had received prior autologous stem cell transplantation.
    - The median time from leukapheresis to product availability was 33 days (range 26-49 days).
  - Efficacy was established based on overall response rate (ORR), complete response rate (CR), 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.

KarMMa; NCT 03361748	
Response Rate	**Abecma-treated population N=100**
Overall Response Rate (sCR+VGPR+PR), n (%) [95% CI]	72 (72) [62, 81]
sCR[a], n(%) [95% CI]	28 (28) [19, 38]
VGPR, n (%) [95% CI]	25 (25) [17, 35]
PR, n (%) [95% CI]	19 (19) [12, 28]
Duration of Response (DOR)	
Duration of Response (PR or better) n Median (months) [95% CI]	 72 11.0 [10.3, 11.4]
Duration of Response for sCR n Median (months) [95% CI]	 28 19.0 [11.4, NE]
Median follow-up for DOR	10.7 months

NE = not estimable, PR = partial response, sCR = stringent complete response, VGPR = very good partial response

[A] All complete responses were stringent CRs

  - Median overall survival (OS) was 19.4 months, and at 12 months the OS rate was 78%. OS data are still immature.

- Boxed warnings:
  - Cytokine Release Syndrome (CRS):
    - CRS occurred in 85% (108/127) of patients. Grade 3 or higher CRS occurred in 9% of patients, with Grade 5 CRS reported in one (0.8%) patient.
    - One patient had fatal CRS. Incidence was higher in the 450 x 10^6 CAR-positive T cell cohort than the 300 x 10^6 cohort.
    - The median time-to-onset of CRS, any grade, was 1 day (range 1 to 23 days), and the median duration of CRS was 7 days (range 1 to 63 days).
    - Treatment for severe CRS includes tocilizumab and corticosteroids along with supportive care.
  - Neurologic Toxicities, which may be severe or life-threatening, occurred following treatment with Abecma, including concurrently with CRS, after CRS resolution, or in the absence of CRS.
    - Neurologic toxicities occurred in 28% of patients receiving Abecma, including grade 3 in 4% of patients.
    - One patient had ongoing Grade 2 neurotoxicity at the time of death, two patients had ongoing Grade 1 tremor at the time of data cutoff.
    - Median time to onset of neurotoxicity was 2 days.
    - Neurotoxicity resolved in 33 of 36 (92%), with median duration of 5 days.
    - Monitor patients for signs of neurotoxicity and manage with supportive care and/or corticosteroids.
  - Hemophagocytic Lymphohistiocytosis (HLH)/ Macrophage activation syndrome (MAS)
    - HLH/MAS occurred in 4% of patients.
    - Incidence was higher in the 450 x 10^6 CAR-positive T cell cohort. All events had onset within 10 days of receiving Abecma, with a median onset of 7 days.
  - Prolonged cytopenia
    - In the KarMMa study, 41% of patients experienced prolonged Grade 3 or 4 neutropenia and 49% experienced prolonged Grade 3 or 4 thrombocytopenia. Median time to recovery was 1.9 months for prolonged neutropenia and 2.1 months for prolonged thrombocytopenia.
    - Three patients underwent stem cell therapy for hematopoietic reconstitution due to prolonged cytopenia. Two of the three patients died from complications of prolonged cytopenia, which occurred in the setting of ongoing or prior severe CRS or HLH/MAS.
    - Monitor blood counts prior to and after Abecma infusion.
  - Only available through the Abecma REMS program
    - Certified healthcare facilities that dispense and administer Abecma must be enrolled and comply with REMS requirements.
    - Certified healthcare facilities must have on-site, immediate access to tocilizumab. Ensure a minimum of 2 doses are available for each patient for infusion within 2 hours of receiving Abecma.
    - Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense, or administer Abecma are trained in the management of CRS and neurologic toxicities.
- Contraindications: none
- Warnings:
  - Hypersensitivity reactions may occur with infusion of Abecma, including anaphylaxis.
  - Abecma should not be administered to patients with active infections or inflammatory disorders.
  - Hypogammaglobulinemia: monitor immunoglobulin levels after Abecma treatment.
  - Secondary malignancies: monitor life-long after Abecma treatment.
  - Patients should refrain from driving and engaging in hazardous occupations or activities for at least 8 weeks following infusion.

- Adverse Reactions (incidence ≥ 20%): diarrhea, nausea, fatigue, pyrexia, edema, CRS, hypogammaglobulinemia, infections (pathogen unspecified), decreased appetite, musculoskeletal pain, encephalopathy, headache, and cough.

Price Per Unit (WAC):

- $419,500 for a one-time infusion.

Therapeutic Alternatives:

- Abecma is the fifth CAR-T cell therapy to be approved by the FDA, however it is the only CAR-T therapy with an indication for multiple myeloma.
- Abecma is intended to be administered in an outpatient setting at a healthcare facility registered with the Abecma REMS program. The manufacturer offers the Cell Therapy 360® program to patients which includes enrollment assistance, financial support, and post-treatment monitoring consisting of a patch to monitor body temperature and a smartphone app.
- Below is a table comparing serious adverse events and cost with other CAR-T therapies:

CAR-T Cell Therapies	Abecma®	Kymriah®	Yescarta®	Tecartus®	Breyanzi®
Incidence of CRS	85%	74-79%	88-94%	91%	46%
Incidence of Neurological Toxicities	28%	58-72%	81-87%	81%	35%
Cost per infusion WAC	$419,500	$373,000	$399,000	$399,000	$410,300
Manufacturer	Bristol-Myers Squibb	Novartis	Kite Pharma, Inc	Kite Pharma, Inc	Bristol-Myers Squibb

- MM is mainly treated with 5 different types of medications: alkylators, CD-38 binding antibodies, immunomodulatory drugs, proteasome inhibitors, and steroids. Many treatment options are available. Choice of therapy depends on prior therapies used, duration of responses, comorbidities, risk, and costs. Common regimens are:
  - Bortezomib/lenalidomide/dexamethasone
  - Bortezomib/cyclophosphamide/dexamethasone
  - Carfilzomib/lenalidomide/dexamethasone
  - Daratumumab/lenalidomide/dexamethasone
  - Ixazomib/lenalidomide/dexamethasone
  - Pomalidomide/botezomib/dexamethasone
- Almost all patients who respond to initial treatment will relapse and need further therapy, while some will not respond to therapy.

Prior Authorization Approval Criteria:

Must meet the following criteria:

Initial Therapy:

- Prescribed by or in consultation with an oncologist, hematologist, or other specialist in the treated disease state **AND**
- Participant aged ≥ 18 years **AND**
- Participant is not currently pregnant **AND**
- Documented diagnosis of relapsed or refractory multiple myeloma (ICD10 C90.00 or C90.02) **AND**
- Documentation of four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody AND
- Participant must be refractory to last treatment regimen **AND**
- No previous history of CAR-T cell therapy **AND**
- No active infections or inflammatory disorders.

Continuation of Therapy:

- None

	Additional Provider Diagnostic/Monitoring Criteria, if desired: • Participant has an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1 (patient must be healthy enough to participate in the pre-treatment lymphodepleting chemotherapy regimen and the collection and cultivation [leukapheresis] process as well as to withstand potential cytokine release syndrome, neurologic toxicities, and prolonged cytopenias). • Abecma has not been studied in patients with a creatinine clearance of less than or equal to 45 ml/minute, alanine aminotransferase >2.5 times upper limit of normal, left ventricular ejection fraction <45%, absolute neutrophil count <1000 cells/mm^3, and platelet count <50,000/mm^3. • CMV infection resulting in pneumonia and death has occurred following Abecma administration. Perform screening for CMV, HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing. Consider antiviral therapy to prevent viral reactivation. • Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Abecma treatment, and until immune recovery following treatment.
Implication to State Medicaid Program:	• LOE: N/A • Ciltacabtagene autoleucel (Janssen) is another CAR-T cell therapy currently being studied for the treatment of relapsed or refractory multiple myeloma. Interim data from a Phase 1/2 (CARTITUDE-1) study of treatment with cilta-cel demonstrated an overall response rate of 97%, with 67% of patients achieving a stringent complete response. This product will compete with Abecma if approved. • Abecma is being studied as an option in earlier lines of therapy for RRMM. • In the KarMMa study, 28 patients (22% of treated population) were retreated after disease progression. Limited data were available on the characteristics of these patients and their associated outcomes, however progression-free survival in these patients was generally poor with a median of one month following treatment. • According to an Institute for Clinical and Economic Review (ICER) report on CAR T-cell therapy in RRMM, both KarMMa and CARTITUDE-1 did not include patients who did not receive therapy in their results. Since manufacturing failures are now rare, most patients who were enrolled but not able to receive treatment likely had more severe or more aggressive disease. Thus, it is likely that accounting for these patients would diminish the benefits seen with the products. In the ICER report, analyzing the data in an intent to treat (ITT) manner results in decrease in ORR from 73% to 63% in KarMMa and 97% to 75% in CARTITUDE-1. • ICER's recommended health-benefit price benchmark (HBPB) range for Abecma is $192,000-$265,000 per dose, which would require a 37%-54% discount in current price. The HBPB for ciltacabtagene autoleucel is $317,000-$475,000 though this finding is preliminary.

References:

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