Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
Office of Tissues and Advanced Therapies

NDA/BLA #s: 125736
PRODUCT: ABECMA (idecabtagene vicleucel), suspension for intravenous infusion
APPLICANT: Celgene Corporation
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Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultation between the Office of Tissues and Advanced Therapies and the Office of Biostatistics and Epidemiology, we have determined that a REMS that includes elements to assure safe use (ETASU) is necessary for ABECMA (idecabtagene vicleucel) to ensure that the benefits of the drug outweigh the risks of cytokine release syndrome (CRS) and neurologic toxicities. During the pre-market evaluation of this product, CRS and neurologic toxicities occurred in 85% and 28% of subjects respectively, including ≥ Grade 3 events in 9% and 4% of subjects respectively. One death due to CRS was reported as well.

Due to the severe adverse events of CRS and neurologic toxicities, which will both be included in a boxed warning on the Prescribing Information (PI), ETASU B and ETASU C will be required to ensure that the drug's benefits outweigh its risks. The REMS for ABECMA (idecabtagene vicleucel) requires that hospitals and their associated clinics that dispense ABECMA are specially certified and have on-site, immediate (within 2 hours) access to tocilizumab. Furthermore, the REMS requires that as part of certification, those who prescribe, dispense, or administer ABECMA are trained about the management of CRS and neurologic toxicities. ABECMA will be dispensed only in certified hospitals and their associated clinics. The certified hospitals and their associated clinics will be required to put processes and procedures in place to ensure that healthcare providers who prescribe ABECMA review the ABECMA Prescribing Information (PI) and are aware of the patient monitoring instructions in the ABECMA PI. Hospital certification will also entail providing patients with information on CRS and neurologic toxicity and informing them of the importance of staying within 2 hours of the certified hospital where they received

ABECMA for approximately 4 weeks after receiving ABECMA treatment, so that they can return to the treatment site for the treatment of CRS or neurologic toxicity, if needed.

In reaching this determination, we considered the following:

A. ABECMA (idecabtagene vicleucel), a B-Cell Maturation Antigen (BCMA)-directed, genetically modified autologous chimeric antigen receptor CAR-T cell immunotherapy, will be licensed to treat 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.

B. Data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) estimated 32,270 new cases of multiple myeloma and 12,830 deaths due to multiple myeloma in the United States in 2020. Multiple myeloma is the second most common hematological malignancy representing 17% of all hematological malignancies and 1.8% of all new cancer cases in the US.[1] The current standard of care for the first-line treatment for multiple myeloma is induction therapy followed by autologous stem cell transplantation (ASCT) and maintenance therapy. Patients ineligible for transplantation receive 8-12 cycles of initial therapy with a triplet or doublet regimen followed with maintenance therapy until progression or toxicity. Treatment options for relapsed and refractory myeloma include ASCT, new anti-myeloma therapy or rechallenge with previous regimen. Almost all patients with multiple myeloma will eventually relapse and require further therapy. Although therapy for patients with relapsed and refractory myeloma has considerably improved in the last several years with approval of multiple new therapies, the 5-year survival rate for multiple myeloma is 54% in the United States.[1] Patients who are refractory to, or have relapsed after, commonly used drugs such as an immunomodulating agent, proteasome inhibitor, and CD38 monoclonal antibodies demonstrate low response rates and have poor prognosis.[2]

C. The pre-specified primary endpoint for the pivotal licensure trial was overall response rate (ORR) following ABECMA (idecabtagene vicleucel) administration. In the pivotal study, MM-001, a total of 127 subjects (efficacy analysis was performed using data cutoff of January 14, 2020) were treated with ABECMA (idecabtagene vicleucel). Of these 127 subjects, 100 subjects (79%) received the approved dose of 300-460 x 10^6 CAR-positive T cells. ORR (95% CI) was 72% (62%, 80%), with complete response (CR) (95% CI) rate of 28% (19%, 37%). The estimated median duration of response (DOR) was 11 months (95% CI: 10.3, 11.4) and median follow-up for DOR was 10.7 months (0.03+ to 19.7+). Efficacy was established based on overall response rate (ORR), complete remission (CR) rate and duration of response (DOR), as determined by an independent review committee. These results demonstrate substantial efficacy of ABECMA in this disease population.

D. Patients who have relapsed and refractory multiple myeloma will be treated with this therapy at hospitals and their associated facilities that are certified under the REMS program. Patients will undergo an apheresis procedure to obtain peripheral blood mononuclear cells. These cells will be sent to Celgene S12 manufacturing facility, where a lentiviral vector is used to encode chimeric antigen receptor T cells. The cells will be

shipped back to the treating hospital. Patients will receive lymphodepletion chemotherapy with fludarabine and cyclophosphamide and will then get a single intravenous dose of ABECMA derived from their T cells. The dose range is a total of 300-460 $\times 10^6$ CAR-positive T cells.

E. Patients with multiple myeloma do not have a baseline incidence of CRS or neurologic toxicity. In the MM-001 study, 127 subjects (original data cutoff of October 16, 2019) were evaluable for safety. CRS occurred in 85% (108/127) of subjects treated with ABECMA (idecabtagene vicleucel), with 9.4% experiencing grade 3 or higher CRS (modified Lee criteria 2014)[3]. There was one fatal event due to CRS. CRS results in a constellation of inflammatory symptoms ranging from a flu-like syndrome to severe multi-organ system failure and death. Specifically, grade 3 or higher CRS requires treatment in an intensive care unit (ICU) setting with oxygenation supplementation and/or mechanical ventilation, vasopressor support along with tocilizumab and/or corticosteroids. In the clinical trial, CRS had a median time to onset of 1 day (range 1-23 days) after infusion with ABECMA (idecabtagene vicleucel) and resolved in 107 of 108 patients with a median duration of 6.5 days (range 1-63 days). Neurologic toxicity occurred in 28% (36/127) of patients with grade 3 or higher toxicity in 4% (5/127) of patients. One patient had Grade 2 neurologic toxicity ongoing at death. Two patients (with Grade 1 tremor) had neurologic toxicity reported as ongoing at the time of data cutoff. Onset of neurologic toxicity was within 8 weeks of ABECMA infusion in all patients. The most common neurologic adverse events included encephalopathy, tremor, aphasia, delirium, motor dysfunction, headache and ataxia. Median time to onset of neurologic toxicity was 2 days (range 1-42 days) after infusion of ABECMA (idecabtagene vicleucel) and resolved in 33 of 36 patients with a median duration of 5 days (range 1-61 days). 34 of 127 (27%) patients had both CRS and neurologic toxicity. There is a boxed warning for CRS and neurologic toxicity. In addition to CRS and neurotoxicity, section 5 "Warnings and Precautions" will include the following: hemophagocytic lymphohistiocytosis (HLH)/ Macrophage activation syndrome (MAS) syndrome, hypersensitivity reactions, serious infections, prolonged cytopenias, hypogammaglobulinemia, secondary malignancies and effects on ability to drive and operate machinery.

F. ABECMA (idecabtagene vicleucel) is not a New Molecular Entity. FDA notes, however, that FDA's definition of "New Molecular Entity" is generally not applicable to biological products licensed under section 351(a) of the Public Health Service Act (PHS Act), such as ABECMA. ABECMA is the subject of an original Biologics License Application under section 351(a) of the PHS Act. It is the first product in the class of BCMA-directed genetically-modified autologous T-cell immunotherapies. ABECMA is made with CAR T technology, which is not a new technology and has been used in four products in another product class.

The REMS will consist of elements to assure safe use, including that hospitals and their associated clinics that dispense ABECMA must be specially certified, and ABECMA must be dispensed to patients only in specially certified hospitals and their associated clinics, with an implementation system, and a timetable for submission of assessments of the REMS.

References:

1. Cancer Stat Facts: Myeloma : National Cancer Institute, Surveillance, Epidemiology, and End Results Program.
2. Gandhi U.H, Cornell R.F, et al. Outcomes of Patients with Multiple Myeloma Refractory to CD38-Targeted Monoclonal Antibody Therapy. Leukemia. 2019 September; 33 (9): 2266-2277.
3. Lee D, Gardner R et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014, July 10, 124(2):188-95.
4. Shaji K, Anderson K et al. International myeloma working group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncology 2016:17:e 328-46