

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**

BLA: 125746/0
PRODUCT: CARVYKTI (ciltacabtagene autoleucel), suspension for intravenous infusion
APPLICANT: Janssen Biotech, Inc.
FROM: Wilson W. Bryan, MD; Director,
Office of Tissues and Advanced Therapies
DATE: February 28, 2022

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 CARVYKTI (ciltacabtagene autoleucel) to ensure that the benefits of the drug outweigh the risks of cytokine release syndrome (CRS) and neurological toxicities (NT). During the pre-market evaluation of this product, CRS, and NT (includes immune effector cell associated neurotoxicity (ICANS) syndrome and other non-ICANS neurological toxicities) occurred in 95% and 26% of patients respectively, including \geq Grade 3 events in 5% and 11% of subjects respectively. One death due to CRS and three deaths due to neurological toxicity were reported.

Due to the severe adverse events of CRS and NT, which will 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 CARVYKTI (ciltacabtagene autoleucel) requires that hospitals and their associated clinics that dispense CARVYKTI 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 CARVYKTI are trained about the management of CRS and neurological toxicities. CARVYKTI 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 CARVYKTI review the CARVYKTI Prescribing Information (PI) and are aware of the patient monitoring instructions in the CARVYKTI PI. Hospital certification will also entail providing patients with information on CRS and NT and informing them of the importance of staying within 2 hours of the certified hospital where they received CARVYKTI for approximately 4 weeks after receiving CARVYKTI treatment, so that they can return to the treatment site for the treatment of CRS or NT, if needed.

In reaching this determination, we considered the following:

- A. CARVYKTI (ciltacabtagene autoleucel), a B-Cell Maturation Antigen (BCMA)-directed, genetically modified autologous chimeric antigen receptor CAR-T cell immunotherapy. It is anticipated to be licensed to treat adult patients with relapsed or refractory multiple myeloma after 4 or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, 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 who are ineligible for transplantation receive 8-12 cycles of initial therapy with a triplet or doublet regimen followed by 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 CARVYKTI (ciltacabtagene autoleucel) administration. In the pivotal study, 68284528MMY2001 (CARTITUDE 1), a total of 97 subjects¹ (efficacy analysis was performed using data cutoff of February 11, 2021) were treated with CARVYKTI (ciltacabtagene autoleucel). All 97 patients received CARVYKTI at the median dose of 0.71×10^6 CAR-positive viable T-cells/kg in the approved dose range of $0.5 - 1.0 \times 10^6$ CAR-positive T-cells/kg.

ORR (95% CI) was 98% (93%, 100%), with stringent complete response (sCR) (95% CI) rate of 78% (71%, 88%). The estimated median duration of response (DOR) was 21.8 months (95% CI: 21.8, NE) and median follow-up for DOR was 23.6 months (22.8, 26.2). Efficacy was established based on the overall response rate (ORR), stringent complete response (sCR) rate, and duration of response (DOR), as determined by an independent review committee. These results demonstrate substantial efficacy of CARVYKTI 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 Janssen 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 CARVYKTI derived from their T cells. The dose range is $0.5-1.0 \times 10^6$ CAR-positive viable T cells per kg of body weight, with a maximum dose of 1×10^8 CAR-positive viable T cells per single infusion.
- E. Patients with multiple myeloma do not have a baseline incidence of CRS or NT. In the CARTITUDE-1 study, 97 subjects (original data cutoff of September 1, 2020) were evaluable for safety. CRS occurred in 95% (92/97) of subjects treated with CARVYKTI (ciltacabtagene autoleucel), with 5% experiencing grade 3 or higher CRS (ASTCT 2019 criteria)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 7 days (range 1-12 days) after infusion with CARVYKTI (ciltacabtagene autoleucel) and resolved in 91 of 92 patients with a median duration of 4 days (range 1-40 days). One patient died of CRS/HLH (hemophagocytic lymphohistiocytosis) after a CRS duration of 97 days.

NT² occurred in 26% (25/97) of patients with grade 3 or higher toxicity in 11% (11/97) of patients. ICANS was observed in 22 patients. Other manifestations of NT included: n=5 NT with parkinsonism, n=6 with peripheral neuropathy and n=3 with cranial nerve palsy- all attributed to the product. Of the 10 patients in whom NT did not resolve, 3 died of NT: 2 from ICANS and 1 from NT with parkinsonian features. Onset of NT was within 8 weeks of CARVYKTI infusion in all but 1 patient. The most common neurological adverse events included, encephalopathy, aphasia, ataxia, peripheral neuropathy, headache, delirium, micrographia, parkinsonism and tremor. Median time to onset of NT was 8 days (range 2-101 days) after infusion of CARVYKTI (ciltacabtagene autoleucel) and resolved in 15 of 25 patients with a median time to resolution of 8 days (range 2-208 days). Median duration of NT in all patients including those with fatal events and NT ongoing at death or last alive date was 62 days (range 2 to 926 days). ICANS occurred in 23% of patients including Grade 3 or higher events in 5% of

patients. Median time to onset of ICANS was 8 days (range 1 to 28 days). ICANS resolved in 17 of 22 patients (77%) with a median time to resolution of 6 days (range 2 to 143 days). Median duration of ICANS in all patients including those who died or had ICANS ongoing at death from another cause or last alive date was 7.5 days (range 2 to 927 days).

CRS and NT along with other serious adverse reactions are included in the boxed warning of CARVYKTI label. In addition to CRS and NT, section 5 “Warnings and Precautions” will include the following: hemophagocytic lymphohistiocytosis (HLH)/ Macrophage activation syndrome (MAS) syndrome, hypersensitivity reactions, serious infections, prolonged and recurrent cytopenias, hypogammaglobulinemia, secondary malignancies and effects on ability to drive and operate machinery.

- F. CARVYKTI (ciltacabtagene autoleucel) 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 CARVYKTI. CARVYKTI is the subject of an original Biologics License Application under section 351(a) of the PHS Act. It is the second product in the class of BCMA-directed genetically modified autologous T-cell immunotherapy. CARVYKTI is made with CAR T technology, which is not a new technology and has been used in previously approved CAR T products from two existing product classes (CD19-directed and BCMA-directed T-cell immunotherapies).

The REMS will consist of elements to assure safe use, including assurance that hospitals and their associated clinics that dispense CARVYKTI must be specially certified, and CARVYKTI 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 DW, Santomasso BD et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant* 2019, 25: 625-638
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

¹Ninety-seven subjects include 80 subjects who received CARVYKTI (commercial product) and 17 subjects who received the same investigational product but were deemed to receive “manufacturing failures” either because the drug product they received did not meet CARVYKTI release specifications or data were not available to make such a determination. The non-proprietary term ciltacabtagene autoleucel (cilta-cel) has been used to reflect this in CARVIKTY label when referencing the safety and efficacy data obtained from 97 subjects, while the term CARVYKTI has been used elsewhere.

²NT includes immune cell-associated neurological syndrome (ICANS) and non-ICANS neurological toxicity (e.g., parkinsonism, peripheral neuropathy, Guillain-Barre syndrome, and cranial nerve palsy). Note, for CAR T products prior to CARVYKTI, NT was used to describe what is now termed ICANS.