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: 125703
Products: TECARTUS (brexucabtagene autoleucel), suspension for intravenous infusion
APPLICANT: Kite Pharma
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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 TECARTUS (brexucabtagene autoleucel) to ensure that the benefits of the drug outweigh the risks of cytokine release syndrome (CRS) and neurological toxicities. The applicant proposed a single consolidated REMS program, the YESCARTA (axicabtagene ciloleucel) and TECARTUS (brexucabtagene autoleucel) REMS Program, to mitigate risks of CRS and neurological toxicities associated with YESCARTA and TECARTUS due to similar risk profiles of these products. Over 90% of patients developed CRS during the pre-market evaluation of TECARTUS, and one CRS-related death was noted. Furthermore, many patients required intensive-care level facilities and the specific use of the monoclonal antibody tocilizumab to manage CRS. Additionally, 80% of all patients experienced neurological toxicities with the majority occurring concurrently with CRS.

Due to the severe adverse events of CRS and neurological toxicities, which will both be included in a boxed warning on the Prescribing Information (PI) for TECARTUS, ETASU B and ETASU C will be required to ensure that the drug's benefits outweigh the risks. The REMS for TECARTUS (brexucabtagene autoleucel) requires that hospitals and their associated clinics that dispense TECARTUS 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 TECARTUS (brexucabtagene autoleucel) are trained about the management of CRS and neurological toxicities according to the YESCARTA and TECARTUS REMS Adverse Management Reaction Guide that is part of the YESCARTA and TECARTUS REMS Training Program for Hospitals. TECARTUS (brexucabtagene autoleucel) 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 TECARTUS review the TECARTUS Prescribing Information and are aware of the patient monitoring instructions in the TECARTUS Prescribing Information. Hospital certification will also entail providing patients with information on CRS and neurological toxicity and informing them of the importance of staying within 2 hours of the certified hospital where they received TECARTUS for approximately 4 weeks after receiving TECARTUS treatment, unless otherwise indicated by their doctor, so that they can return to the treatment site for the treatment of CRS or neurological toxicity, if needed.

In reaching this determination, we considered the following:

A. TECARTUS (brexucabtagene autoleucel), a CD19-directed, genetically modified autologous T cell immunotherapy, will be licensed to treat adult patients with relapsed or refractory mantle cell lymphoma. Mantle cell lymphoma (MCL) is a rare subtype of non-Hodgkin lymphoma (NHL) that represents 3-10% (SEER 2017) of all new non-Hodgkin lymphoma cases per year. The estimated incidence of MCL is 0.51 to 0.55 cases per 100,000 persons in the US. Most patients present with aggressive, disseminated disease and there is a 2.5:1 male-to-female predominance with a median age at diagnosis of 64 years.[1,2] Generally, MCL is thought to possess the worst characteristics of both indolent and aggressive NHL subtypes due to the incurability of the disease with conventional chemotherapy and a more aggressive disease course in most patients.

B. The prognosis for patients who are diagnosed with MCL is poor, with the median duration of remission after standard chemoimmunotherapy regimens of 1.5-3 years and the median overall survival of 3-6 years.[3]

C. The pre-specified primary endpoint for the pivotal licensure trial was overall response rate (ORR) during the 6 months following TECARTUS (brexucabtagene autoleucel) administration. In the pivotal study, ZUMA-2, a total of 82 subjects were enrolled and treated with TECARTUS (brexucabtagene autoleucel). Of the 60 subjects whose data were evaluable for efficacy, the ORR (95% CI) was 87% (75, 94), with complete remission (CR) of 62% (48,74) and partial remission (PR) of 25% (15, 38). The median duration of response (DOR) was not reached. Efficacy was established on the basis of the overall response rate with subjects in CR primarily contributing to the durability of the response (DOR), as determined by an independent review committee. These results demonstrate substantial efficacy of TECARTUS over available therapies in this disease population.

D. Patients who have relapsed or refractory MCL will be treated with this therapy within certain hospitals and their associated clinics that are accredited by the Foundation for the Accreditation of Cellular Therapy (FACT). Patients will undergo an apheresis procedure to obtain peripheral blood mononuclear cells. These cells will be (b) (4) and will be sent to a

Kite Pharma manufacturing facility, where a retroviral vector is used to encode chimeric antigen receptor (CAR) T cells. The cells will be shipped back to the treating hospital. Patients will receive lymphodepletion chemotherapy, and will then get a single intravenous dose of TECARTUS (brexucabtagene autoleucel) derived from their T cells. The dose is 2×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 CAR-positive viable T cells.

E. Patients with MCL do not have a baseline incidence of cytokine release syndrome. Neurological toxicities that were observed with the product as detailed below, were not associated with mantle cell lymphoma or prior therapies. In the ZUMA-2 study, of the 82 subjects whose data were evaluable for safety, 91% (75/82) of subjects treated with TECARTUS (brexucabtagene autoleucel) experienced CRS and 18% had Grade ≥3 CRS (modified Lee criteria 2014) that included one fatal CRS event. 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 CRS requires treatment in an intensive care unit (ICU) setting with broad-spectrum antibiotics, oxygenation supplementation and/or mechanical ventilation, and multiple vasopressors along with tocilizumab. In the clinical trial, CRS generally developed within the first 13 days after infusion with TECARTUS (brexucabtagene autoleucel) and the median CRS duration was ten days. Additionally, 81% (66/82) of subjects experienced neurological toxicity within 8 weeks of YESCARTA infusion, with 37% experiencing Grade ≥3 toxicity. The most common neurological toxicity events included encephalopathy, headache, tremor, aphasia, and delirium. Serious or fatal events including cerebral edema, leukoencephalopathy and seizures were reported with TECARTUS. Neurological toxicity events developed within the first 31 days, and the median duration was 21 days. Almost all Grade ≥2 neurotoxicity events, which necessitate treatment with steroids, occurred during the first seven days post-infusion. Neurological toxicities occurred during CRS or after CRS resolution and had longer time to resolution as compared to CRS. Few neurological toxicity events occurred in subjects who did not experience CRS. In addition to the boxed warning for CRS and neurological toxicity, the PI will contain the following adverse reactions within Warnings and Precautions: hypersensitivity reactions, serious infections, prolonged cytopenia, hypogammaglobinemia, secondary malignancies and impaired ability to drive and operate machinery.

F. TECARTUS (brexucabtagene autoleucel) was given a breakthrough designation in the IND phase. TECARTUS is the third product in class CD19-directed genetically-modified autologous Tcell immunotherapy. TECARTUS is not a New Molecular Entity (NME).

YESCARTA (axicabtagene ciloleucel), a CD19-directed, genetically modified autologous T cell immunotherapy was licensed on October 18, 2017 to treat adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Due to the serious risks of CRS and neurological toxicities associated with YESCARTA (axicabtagene ciloleucel), it was approved with a REMS. The YESCARTA REMS includes goals and elements to assure safe use identical to those necessary for the safe use of TECARTUS. In order to minimize burden on the healthcare delivery system [section 505-1(f)(2)(D)], the REMSs for

YESCARTA and TECARTUS will be a shared system REMS to encompass both drugs in a single REMS program.

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

References

1. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017

2. Swerdlow, S. H. (2016). The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood, 127*(20), 2375-2390.

3. Vose, J. M. (2017). "Mantle cell lymphoma: 2017 update on diagnosis, risk-stratification, and clinical management." Am J Hematol **92**(8): 806-813.