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:	125646
Products:	Kymriah (tisagenlecleucel), suspension for intravenous infusion
APPLICANT:	Novartis
FROM:	Wilson Bryan, MD; OTAT Office Director
DATE:	August 2, 2017

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 Kymriah (tisagenlecleucel) to ensure that the benefits of the drug outweigh the risks of cytokine release syndrome (CRS) and neurotoxicity. During the review of this application, FDA determined that the Applicant's proposed REMS, which consisted of a communication plan for healthcare providers, was not adequate to mitigate these risks. Over 70% of patients developed CRS during the pre-market evaluation of this product, and many required intensive-care level facilities and the specific use of the monoclonal antibody tocilizumab to manage this adverse event.

Due to the severe adverse events of CRS and neurotoxicity, which will both be included in a boxed warning on the label, ETASU B and ETASU C will be required to ensure that the drug's benefits outweigh the risks. The REMS for Kymriah (tisagenlecleucel) will ensure that hospitals and their associated clinics that dispense Kymriah are specially certified and have on-site, immediate (i.e., within 2 hours) access to tocilizumab. The REMS will ensure that as part of certification, those who prescribe, dispense or administer Kymriah (tisagenlecleucel) are trained about neurotoxicity and the management of CRS based on a treatment algorithm that is part of the site training material. Site-certification will also entail providing patients with information on CRS and neurotoxicity and informing them of the importance of staying close to the certified

hospital or associated clinic after receiving Kymriah, so that they can return to the treatment site for the treatment of CRS if needed. Kymriah will only be dispensed to patients in certain health care settings, specifically, hospitals and their associated clinics.

In reaching this determination, we considered the following:

A. Kymriah (tisagenlecleucel), a genetically modified autologous immunotherapy, will be licensed to treat cases of relapsed and refractory B cell acute lymphoblastic leukemia (ALL) in ages 3-25 years. The incidence of new cases of pediatric ALL is approximately 3,100 in children and adolescents per year (PDQ, HCP April 2017[1]). Approximately 620 pediatric and young adult patients with ALL relapse each year in the United States after achieving an initial response (Maude et al. 2015[2]). Current treatment for de novo or relapsed B cell ALL includes combinations of chemotherapy, radiation therapy, and hematopoietic stem cell transplantation (HSCT).

B. Survival after relapse depends on the timing and type of the relapse. Relapses that occur within 18 months of initiation of therapy or while the patient is still on therapy have an extremely poor prognosis despite subsequent therapy. The only potential cure for relapse in recurrent pediatric ALL has been HSCT. For HSCT to succeed, the patient needs to be in complete remission with no minimal residual disease which is difficult to achieve after relapse. Overall, the prognosis for relapsed and refractory B cell ALL is very poor.

C. The pre-specified primary endpoint for the pivotal licensure trial was overall remission rate (ORR) during the 3 months after Kymriah (tisagenlecleucel) administration. The pivotal study enrolled 88 subjects, 63 of whom were infused with Kymriah (tisagenlecleucel) manufactured in the U.S. facility. A total of 52 subjects (82.5%) of 63 in the efficacy analysis set had an overall disease response of complete remission, and the result was statistically significant. The median time follow-up time for duration of response (DOR) was 4.8 months. The median DOR has not been reached. Below is a table of products that have been previously approved or licensed to treat relapsed and refractory B cell acute lymphoblastic leukemia (ALL) for this population. **Table: FDA Approved Therapies for R/R ALL in Pediatric and Young Adult Patients**

FDA-Approved Products	Approval/ Year	Results
Clofarabine (CLOLAR)	2004, accelerated	CR 11.5%
Vincristine lyophilized injection (MARQIBO)	2012, accelerated	CR 4.6%
Blinatumomab	2014	CR 17.1%; Median DOR 6.0

[1] https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0032725/

[2] Maude SL, Teachey DT, Porter DL, et al (2015) CD19-targeted chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. Blood; 125:4017-23.

FDA-Approved Products	Approval/ Year	Results
(BLINCYTO)		months
Inotuzumab ozogamicin (BESPONSA)	2017	CR 35.8%; Median DOR 8.0 months

CR: complete remission; DOR: duration of response;
Source: USPI for CLOLAR, BLINCYTO, MARQIBO, BESPONSA

D. Patients between the ages of 3 and 25 years who have relapsed or refractory B cell ALL will be selected for this therapy within certain hospitals, which Novartis has chosen and have been accredited by the Foundation for the Accreditation of Cellular Therapy (FACT). They will have a pheresis procedure to obtain peripheral blood mononuclear cells. These are frozen and sent to a Novartis manufacturing facility, where a lentiviral vector will be used to encode chimeric antigen receptor T cells from the drawn blood. This will then be shipped back to the ordering facility. The patient will be given lymphodepletion therapy, and will then get a single intravenous dose of Kymriah (tisagenlecleucel) derived from their T cells. The dose is decided by weight. If under 50 kilograms (kg) 2-5 x 10e6 Kmyriah cells/kg. Greater than or equal to 50 kg., 1-2.5 x 10e8 Kymriah cells as a flat dose. There are no repeat doses.

E. Patients with B cell precursor ALL do not have a baseline incidence of cytokine release syndrome. Neurological toxicity that was observed with the product as detailed below was not associated with ALL or prior therapies. In the pivotal study B2202, 54 of 68 (79%) subjects treated with Kymriah (tisagenlecleucel) experienced CRS, and 33/68 (49%) of the subjects had Grade 3/4 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 3/4 CRS required treatment under ICU settings and based on a treatment algorithm that required use of antipyretics, broad spectrum antibiotics, oxygen supplementation and or mechanical ventilation, and multiple vasopressors along with the use of tocilizumab. The median time to onset of Grade 3/4 CRS was six days. The median duration of Grade 3/4 CRS was 9 days. Of the 54 subjects with CRS, 27 (50%) required 1-3 doses of tocilizumab. In addition, 44 /68 (65%) subjects had neurotoxicity (defined as events such as aphasia, tremor, seizures, confusion, headache, and encephalopathy) within the first 8 weeks, with 12 subjects (18 %) with grade 3 (and none being grade 4). Besides the boxed warning for CRS and neurotoxicity, the label will contain information regarding the following under Warnings: infections, febrile neutropenia, hypogammaglobinemia and impaired driving ability/operate machinery.

F. Kymriah (tisagenlecleucel) has been given a breakthrough designation in the IND phase and is a first in class gene therapy. Kymriah is a first in class CD19-directed genetically-modified autologous T cell immunotherapy. It is not a new molecular entity but it is a new technology and a new biologic class of products.

The REMS will consist of elements to assure safe use, including that hospitals and their associated clinics that dispense Kymriah (tisagenlecleucel) must be certified, and Kymriah

(tisagenlecleucel) must be dispensed to patients only in certain healthcare settings, an implementation system, and a timetable for submission of assessments of the REMS.