Memorandum

BLA 125646/0

Action Due Date: October 3, 2017

Applicant: Novartis

APPROVED
By Bindu George at 2:01

Established Name: Tisagenlecleucel (Trade name: KYMRIAH ™)

From: Bindu George, M.D., Branch Chief, Clinical Hematology Branch, FDA/CBER/OTAT/DCEPT

APPROVED
By Marc Theoret, MD at 11:

Through: Marc Theoret, M.D., Associate Director (Acting) of Immuno-Oncology Therapeutics, Oncology Center of Excellence (OCE)

Date: August 28, 2017

Purpose: To discuss the indication statement in the prescribing information (label)

The primary clinical review of the efficacy and safety of BLA 125646 for KYMRIAH was conducted by Dr. Maura O'Leary with Dr. Donna Przepiorka (team leader). The purpose of this document is to discuss the rationale for the indication statement; in particular, the recommendation to not include in the indication statement that tisagenlecleucel is for use with lymphodepletion (LD) chemotherapy.

Page 46 of the BLA clinical review memorandum discusses the recommendation to include the use of tisagenlecleucel with lymphodepletion chemotherapy in the indication statement of the label. As noted in this review, majority of patients in Study 2202B, received lymphodepletion chemotherapy with insufficient information to conclude that the efficacy of tisagenlecleucel was independent of lymphodepletion (LD) chemotherapy.

I have reviewed the basis for this recommendation in the clinical review memorandum and do not recommend including a requirement for use with LD chemotherapy in the indication statement. Section 14 (Clinical Trials Section) of the label notes that of the twenty two subjects with WBC count <1000/µL, two subjects did not receive LD prior to Kymriah. As noted in page 54 of the clinical review, of the three patients who did not receive LD chemotherapy, one patient achieved a complete remission (CR) at Month 3 (the primary efficacy assessment time point), the second patient's response status was unknown and the third was noted to achieve a CR at Day 28 (pending additional information for response at Month 3 assessment). The sample size of three patients is insufficient to support a robust conclusion of efficacy of but is suggestive of activity of tisagenlecleucel in the absence of LD chemotherapy in the indicated population. In addition, LD chemotherapy was an optional treatment in Study 2202 B, stipulated by the patient's WBC count at the time of the tisagenlecleucel infusion. Furthermore, indication statements are limited to describing the treatment, relief, prevention, mitigation, cure, or diagnosis or manifestations of a recognized disease or condition. LD chemotherapy is not intended to treat or cure refractory or relapsed B cell precursor Acute Lymphoblastic Leukemia (ALL) as there are no FDA approved drugs indicated for lymphodepletion.

Recommendation: The indication statement should not include the requirement for LD chemotherapy with use with tisagenlecleucel.