MEMORANDUM

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FDA / CBER / OTAT / DCEPT

BLA 125646/0	
Submission Date	February 2, 2017
PDUFA ADD	October 3, 2017
Review Date	August 28, 2017
Product/Trade Name	Tisagenlecleucel/ KYMRIAH
Applicant	Novartis
Proposed Indication	KYMRIAH is a CD19-directed genetically-modified autologous T cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse
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Clinical Pharmacology Reviewer	Iftekhar Mahmood, PhD
Statistical Reviewer	Xue (Mary) Lin, PhD (OBE) Shiowjen Lee, PhD (OBE)
Regulatory Project Manager	Erica Giordano
Recommendation	Approval

Executive Summary

Novartis Pharmaceuticals Corporation submitted this Biologics License Application (BLA) for licensure of tisagenlecleucel/KYMRIAH, a CD19-directed genetically-modified autologous T cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

Please see primary reviews for detailed review of this original BLA. The review team recommends approval of this BLA for the above indication, and I concur with the review team's recommendation.

Notable Review Highlights

The results from one multicenter, open-label, single arm-clinical trial, CCTL019B2202 (B2202), conducted under a Special Protocol Assessment, forms the basis for the safety and efficacy assessment of KYMRIAH in pediatric and young adult patients with relapsed or refractory B-cell ALL. Study B2202 is an adequate and well controlled study and provides substantial evidence of effectiveness for the proposed indication.

The primary efficacy endpoint was the overall remission rate (ORR), which included complete remission (CR) and CR with incomplete blood count recovery (CRi). The overall remission rate (ORR) during the 3 months after KYMRIAH administration in the 63 subjects who comprised the Efficacy Analysis Set, was 82.5% and the CR was 63% (95% CI, (50%, 75%). With a median follow-up of 4.8 months, the median duration of CR was not reached. Of note, the ORR following treatment with KYMRIAH is better than what has been reported in patients with relapsed disease, where the average ORR is approximately 40%.

Although there is no question as to the benefit of KYMRIAH, significant risks to subjects were identified in Study B2202. Eighty-four percent (84%) of subjects experienced Grade 3 or greater adverse events. The most concerning were cytokine release syndrome (CRS) and neurologic adverse events, which occurred in 79% and 65% of subjects, respectively. Of note, severe CRS was noted in 49% of subjects, and is considered life threatening, and can be fatal without significant supportive measures, which may include ICU admission, pressure support, mechanical ventilation and/or dialysis. Other adverse events of interest included infections (59%), cytopenias unresolved by Day 28 (38%), and febrile neutropenia (38%).

Although the benefit of KYMRIAH in the studied population is impressive, significant safety concerns were identified that warrant a Risk Evaluation and Mitigation Strategy (REMS) to support a favorable benefit/risk profile. The proposed REMS is based on the Applicant's risk mitigation strategy employed during the study, which included: treatment with an IL-6 receptor antagonist (tociluzimab), on-site training for participating sites, restriction of study sites to transplant centers, and close monitoring of subjects for safety events.

The REMS will be a postmarketing requirement (PMR) and will include Elements to Assure Safe Use (ETASU) for the management of cytokine release syndrome and neurologic toxicity, training and assessment of sites and the use of tocilizumab. An

additional PMR will be a postmarketing observational study to assess short and long-term toxicities of KYMRIAH (B2401).

The overall benefit-risk profile of KYMRIAH is favorable, and the REMS is intended to ensure that the benefits of KYMRIAH outweigh the risks of CRS and neurologic toxicity.

Recommendations

Approval for KYMRIAH for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse is recommended. A REMS with ETASU will be utilized to ensure that the benefit/risk profile is favorable.

APPROVED
By Tejashri Purohit-Sheth, M.D. at 12:43 pm,

APPROVED
By Wilson W. Bryan, M.D. at 1:02 pm,