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Trade Name	Yescarta
Name of Applicant	Kite
Therapeutic Class	To be determined

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) is in response to the consult from the Center for Biologics Evaluation and Research (CBER) on Kite's proposed REMS comprised of a communication plan (CP) submitted for the new Biologics License Application (BLA) 125643 axicabtagene ciloleucel (Yescarta). CBER also requests recommendations from DRISK on a REMS that will mitigate the risks of Cytokine Release Syndrome (CRS) and neurotoxicity.

In the Applicant's non-Hodgkin lymphoma (NHL) clinical trial, prior to initiating treatment, hospitals and prescribers were required to undergo training to understand the risks and management of axicabtagene ciloleucel-related toxicity. If approved, the proposed CP REMS will not ensure that prescribers and hospitals will undergo the appropriate training to mitigate these risks, or ensure that the hospital or treatment site will include safe use conditions necessary to help mitigate the risks of CRS. Based on the serious and severe risks of CRS and neurotoxicity, and the need to have tocilizumab on-site should CRS occur, this reviewer and the CBER reviewer division do not agree with the Applicant that their proposed CP REMS is sufficient to mitigate these risks.

DRISK recommends a REMS that includes elements to assure safe use (ETASU) comprised of hospital certification and documentation of a safe use condition requiring that tocilizumab be available on site prior to initiating treatment. We recommend that prescriber training and education on the symptoms and management of CRS and neurotoxicity occur under the hospital certification element.

1 Background

1.1 PRODUCT INFORMATION

Yescarta is a genetically modified autologous immunocellular therapy with the proposed indication for the treatment of adult patients with relapsed/refractory aggressive B-cell NHL who are ineligible for autologous stem cell transplant (ASCT). The patient is administered a lymphodepleting chemotherapy with cyclophosphamide and fludarabine, the patient's T cells are extracted by leukapheresis and then modified ex vivo by retroviral transduction to express a chimeric antigen receptor (CAR) comprising an anti-CD19 single chain variable fragment linked to CD28 and CD3-zeta co-stimulatory domains. The anti-CD19 CAR T cells are expanded, and then these modified cells are infused back into the patient.

Following anti-CD19 CAR T cell engagement with CD19 expressing target cells, the CD28 and CD3-zeta co-stimulatory domains activate downstream signaling cascades that lead to T-cell activation, proliferation, acquisition of effector functions and secretion of inflammatory cytokines and chemokines. This leads to apoptosis and necrosis of CD19 expressing target cells.

Yescarta is a single, one-time treatment with the target dose of 2×10^6 anti-CD19 CAR T cells/kg body weight (range: (b) (4) cells/kg), with a maximum of 2×10^8 anti-CD19 CAR T cells.

The setting in which the drug is likely to be administered is an inpatient hospital setting or infusion center. The proposed labeling submitted with the application recommends, but does not state that of patients receiving Yescarta infusion must be hospitalized.

Yescarta was granted orphan drug designation on March 27, 2015, and Breakthrough Therapy Designation on December 3, 2015. The Applicant commenced a rolling submission of the BLA application for Yescarta on December 31, 2016, completing the submission March 31, 2017. The Prescription Drug User Fee Act (PDUFA) date is November 29, 2017. Yescarta is currently not marketed in any other jurisdiction.

1.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 125643 relevant to this review:

- 12/03/2015: Breakthrough Therapy Designation (BTD) granted
- 03/31/2017: BLA 125643 rolling submission completed
- 06/08/2017: Information Request (IR) sent to the Applicant based on DRISK Review of CP REMS. The Applicant was asked to submit education and training on the risks of Yescarta that were used in clinical trials.

2 Therapeutic Context and Treatment Options

2.1 DESCRIPTION OF THE MEDICAL CONDITION

Non-Hodgkin lymphoma is the fifth most common cancer in the United States. NHL comprises a group of diseases that vary in clinical course. Among the aggressive subtypes is diffuse large B-cell lymphoma (DLBCL); DLBCL is the most prevalent of the subtypes, representing about 30% to 40% of all NHL diagnoses in adults. The Surveillance, Epidemiology, and End Results (SEER) Program estimated there would be 72,580 new cases of NHL and 20,150 deaths due to NHL in the United States in 2016.^{1,a,b}

2.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The first-line treatment for aggressive B-cell NHL is a regimen of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) in combination with an anti-CD20 monoclonal antibody (mAb) such as rituximab.² This therapy achieves long term disease remission in < 40% of subjects. Patients with relapsed or refractory aggressive B-cell NHL represent 60% or more of all subjects with aggressive B-cell NHL, and refractory/relapsed disease is a challenge in treating these patients, especially patients for whom ASCT is not a treatment option. Objective response rates (ORRs) to second-line chemotherapy in patients with refractory disease range from 0 to 23%.³ About one-half of patients who respond to second-line therapy are able to proceed to ASCT.⁴

^a Section 505-1 (a) of the FD&C Act: FDA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

^b Section 505-1 (a) of the FD&C Act: FDA factor (A): *The estimated size of the population likely to use the drug involved.*

3 Benefit Assessment

The applicant studied Yescarta in a Phase 2, open-label, multi-center, single-arm trial enrolling 111 patients with refractory aggressive B-cell NHL; 101 patients received study drug. A preliminary analysis of Yescarta efficacy was prepared by the Division of Hematology Products clinical reviewer and the statistician for this application, using data submitted by the applicant. Additional efficacy analyses are expected to be performed by the sponsor and the Agency. The objective response rate in the full phase 2 analysis set per investigator was 75% (95% confidence interval [CI], 66, 83), and per independent review committee (IRC) was 65% (95% CI 55, 74). Per IRC, 47% of patients (n=52) had a complete remission (CR), and 18% had a partial remission. With an estimated 6.3 months follow-up for progression-free survival (PFS), the PFS was 5.9 months (95% CI 3.4, 9.9). With an estimated 8.5 months follow-up for overall survival (OS), the estimated median OS was not reached (95% CI, 10.5 months, NE). Review of this application is ongoing at the time of this writing.

4 Risk Assessment & Safe-Use Conditions

Adverse events of special interest reported by the Applicant include CRS and neurological/psychiatric events. In the NHL study, 93% of patients (n=93), experienced CRS, with 13% (n=13) of patients experiencing severe/life threatening \geq Grade 3 CRS. Symptoms of CRS included fever and chills, hypotension, and tachycardia. Events associated with CRS included kidney injury, cardiac failure, atrial fibrillation, ventricular tachycardia, capillary leak syndrome, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome. The median time to onset was 2 days (range 1-12 days), with a median duration of 8 days. One fatality from CRS occurred. Patients with Grade 2 or higher CRS were treated with tocilizumab, and patients with Grade 3 or higher CRS were treated additionally with corticosteroids.

Neurological/psychiatric events occurred in 84% of patients; 31% were classified as a Grade 3 or higher event. The median time to onset was 5 days (range, 1 to 17 days). Commonly occurring specific neurological events included encephalopathy (34%), confusion (29%), aphasia (18%), and somnolence (15%). The proposed labeling recommends treatment of neurological/psychiatric events with tocilizumab (Grade 2 and higher), steroids (Grade 3 and higher), and seizure prophylaxis (Grade 2 and higher). FDA clinical reviewers performed a preliminary analysis of deaths that occurred in the NHL clinical trial. Thirty of the 101 patients who were treated with axicabtagene ciloleucel died. Twenty-five patients died due to disease progression. Two patients died secondary to a combination of disease progression and other drugs used in the treatment of the disease. One patient died secondary to pulmonary embolism without disease progression. This death is classified as unrelated to axicabtagene ciloleucel. Two patients died secondary to adverse reactions to axicabtagene ciloleucel. One of the two therapy-related deaths was secondary to CRS and brain injury, and the other was secondary to CRS and hemophagocytic lymphohistiocytosis activation syndrome. The FDA safety analysis of Yescarta is ongoing.

The review division has discussed including CRS and neurotoxicity in a Boxed Warning and in Sections 5.1 and 5.2 of Warnings and Precautions. Due to the nature and severity of these adverse events, the

review division has concerns that labeling alone may not be sufficient to mitigate the risks of CRS and neurotoxicity of Yescarta.

5 Expected Postmarket Use

Yescarta is expected to only be administered at an inpatient hospital or infusion center. The patient must receive a lymphodepleting chemotherapy prior to receiving the Yescarta infusion. In clinical testing, patients were given fludarabine and cyclophosphamide as the lymphodepleting chemotherapy regimen. Yescarta is prepared from autologous blood of the patient. To prepare Yescarta, a patient's own T cells are harvested and engineered ex vivo by retroviral transduction to express a chimeric antigen receptor (CAR) comprising an anti-CD19 single chain variable fragment (scFv) linked to CD28 and CD3-zeta co-stimulatory domains. The anti-CD19 CAR T cells are expanded and infused back into the patient over 30 minutes. Per the Applicant's clinical testing protocol, patients were hospitalized for the infusion, and remained hospitalized for a minimum of 7 days following the infusion.

5.1 HEALTHCARE SETTING

The Applicant states that they will maintain chain of custody and chain of identity from apheresis pick-up at the apheresis site through manufacturing at the manufacturing facility, and delivery back to the hospital or infusion center to prevent medication errors or administering the drug to the wrong patient.^c Once the product reaches the hospital or infusion center, the healthcare personnel are experienced in matching drugs and blood products to the appropriate patient by usual medical practice.

The Applicant plans to use facilities experienced in bone marrow transplantation to prescribe and administer Yescarta, as was done in the clinical trial. During the clinical trial, training included education on the risks and management of CRS and neurotoxicity. The Applicant's Pharmacovigilance Plan does not detail the training and certification of the leukapheresis and cryopreservation facilities for the safe and effective collection cells, but they expect the product to be used in facilities experienced in bone marrow transplantation. The Applicant does not describe training or certification of hospitals to be able to prescribe and administer Yescarta in the commercial marketing setting, or if they will eventually expand use in facilities not experienced in bone marrow transplantation. In pre-approval clinical testing, the Applicant trained the investigators/health care providers (HCPs) who participated in the Yescarta clinical trials via investigator meetings, site initiation visits, monthly investigator calls, and Dear Investigator Letters (DILs). Training was provided on Yescarta background, trial design, eligibility criteria, procedures and assessments, product logistics, toxicities, and toxicity management recommendations during both the October 2015 Investigator Meeting (IM) and during each site initiation visit. Ongoing training was provided on a monthly basis during the investigator calls.^d It is not clear if participation in the monthly call was required for investigators.

^c Major concerns with infusion of product manufactured for another patient are fatal infusion reactions due to HLA and/or ABO incompatibility, and graft versus host disease.

^d The submission did not detail how investigators absent from the investigator calls received the information presented at the investigator call.

6 Risk Management Activities Proposed by the Applicant

6.1 REVIEW OF APPLICANT'S PROPOSED REMS

The applicant submitted a proposed REMS with the BLA application. The REMS consists of a CP that includes a REMS Letter for HCPs, a REMS letter to professional societies, an Adverse Reaction Management Guide, a Patient Wallet Card, and a REMS Website. The Applicant states that the REMS can be approved without elements to assure safe use (ETASU). They stated the following about why a CP was appropriate and ETASU are not needed:

Kite Pharma is also using the approach used for YERVOY. In March 2011, YERVOY became the first FDA-approved member of a new class of drugs in oncology known as immune checkpoint inhibitors. As a T-cell activating agent, YERVOY was associated with unique adverse reactions (immune-related events), which were not common to other standard anti-cancer medications. As such, HCPs were generally not experienced in managing immune-mediated events. Bristol-Myers Squibb (BMS) and the FDA agreed on a REMS that was based on a communication plan. The objectives of the YERVOY REMS were to inform HCPs about the serious immune-mediated risks associated with YERVOY and to provide guidance on the management of these reactions. The REMS elements included a medication guide on managing immune-mediated events associated with YERVOY and a PWC, which an intended goal that was similar to what is being proposed by Kite Pharma. The YERVOY REMS met its key objectives and was removed in March 2015.

Kite Pharma also considered Elements to Assure Safe Use as a part of the REMS and concluded that these tools were not required to mitigate the risks associated with YESCARTA™. YESCARTA™ will be infused at qualified treatment sites and apheresis centers. The HCPs at these centers are already experienced in using cellular therapies in the form of bone marrow transplantation. Further restriction of the infusion sites or of prescribers is therefore not needed and is unlikely to improve the safe use of YESCARTA™. Kite Pharma has collaborated with the (b) (4) to create a registry as a way to gather safety data on YESCARTA™ to fully characterize the safety profile in the post-marketing period.

The Applicant's REMS submission included a REMS Document and the REMS materials. The submission did not include a REMS Supporting Document, although the REMS Background document submitted contains content that should be included in the REMS Supporting Document.

6.1.1 REMS Goals

The Applicant's goals of the Yescarta REMS are:

- To inform healthcare providers (HCPs) about the potential risk of severe, life-threatening, or fatal cytokine release syndrome (CRS) and neurologic events
- To guide prescribers about the appropriate management of CRS and neurologic events associated with Yescarta
- To ensure that every patient administered Yescarta receives a Patient Wallet Card (PWC)

Reviewer Comments: DRISK does not agree with the proposed goals.

6.1.2 REMS Materials & Key Risk Messages

The Applicant has proposed the following communication tools as part of the REMS.

REMS Letter for HCPs and REMS Letter for Professional Societies

The proposed *REMS Letter for HCPs* and *REMS Letter for Professional Societies* will inform HCPs of the risk of CRS, the serious clinical manifestations associated with CRS and that that CRS may be life-threatening. The letter will also highlight the serious risk of neurological events that have been observed with Yescarta treatment.

REMS Adverse Reaction Management Guide

The REMS Adverse Reaction Management Guide would expand on the same safety information in the REMS Letter for HCPs, and would additionally provide information regarding the management of CRS and neurological events.

Patient Wallet Card

The wallet card would provide information to patients on the signs and symptoms of CRS and neurological events that require immediate medical attention.

REMS Website

The Yescarta REMS Program Website will include links to the REMS materials (PI, REMS letters, REMS Adverse Reaction Management Guide, and Patient Wallet Card).

6.1.3 REMS Assessment Plan

The Applicant's proposed REMS Assessment Plan includes the following:

- Evaluations of HCPs' understanding and patients' understanding of the risks of Yescarta
- A summary of all reported severe, life-threatening CRS and NE with an analysis of adverse event outcomes and treatment. This will be presented within periodic safety reports.
- Assess whether the REMS is meeting its objectives. If the conclusion is that it is not, Kite Pharma will discuss with the Agency ways that the REMS can be modified.

6.2 OTHER PROPOSED RISK MANAGEMENT ACTIVITIES

The Applicant proposed routine pharmacovigilance activities that include:

- Systems and processes that ensure that information about all suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner
- The preparation of reports for regulatory authorities;
 1. Expedited adverse drug reaction (ADR) reports
 2. Periodic safety update reports (PSURs)
 3. Ad hoc requests for aggregate data
 4. Evaluation of safety data for surveillance and signal detection

Reviewer Comments: DRISK acknowledges the other proposed risk management activities; we defer to CBER's Division of Pharmacovigilance for review and input.

7 Discussion

The review of this application is ongoing; however, the clinical reviewer's preliminary analysis is that the efficacy is compelling for providing a clear benefit for the proposed indication. However should this application be approved, the clinical review team and this reviewer recommend risk mitigation strategies beyond labeling to ensure the benefits outweigh the serious risks of CRS and neurotoxicity.

The Applicant's proposed CP REMS is to educate prescribers on the risks of CRS and neurotoxicity by informing prescribers of these risks with the use of communication materials such as letters, an adverse reaction management guide, and distribution of a patient wallet card. The Applicant has proposed a REMS that is similar to the Yervoy (ipilimumab) REMS. Yervoy was approved with a REMS comprised of a communication plan;⁵ Yervoy was approved for the treatment of unresectable or metastatic melanoma. Immune-mediated adverse reactions are included as a boxed warning in the Yervoy product labeling. The most frequently occurring immune-mediated adverse reaction for Yervoy was enterocolitis. Grade 3 to 5 enterocolitis occurred in 7% of patients in clinical testing, and Grade 2 enterocolitis occurred in 5% of patients. In the NHL study of axicabtagene ciloleucel, 93% of patients experienced CRS, with 13% of patients experiencing severe/life threatening \geq Grade 3 CRS.

This REMS proposal differs from the Applicant's risk mitigation actions and support that occurred during the product's NHL clinical trial. During the clinical trial, required training included education on the risks and management of CRS and neurotoxicity. The Applicant's REMS submission does not include training or certification of hospitals to be able to prescribe and administer Yescarta. The Applicant stated that they trained the investigators/HCPs who participated in the Yescarta clinical trials via investigator meetings, site initiation visits, monthly investigator calls, and Dear Investigator Letters. Training was provided on Yescarta background, trial design, eligibility criteria, procedures and assessments, product logistics, and toxicity management recommendations during both the October 2015 Investigator Meeting (IM) and each site initiation visit. Ongoing training was provided on a monthly basis during the investigator calls.

A CP REMS does not ensure that prescribers and hospital will undergo the appropriate training to mitigate the risks of CRS and neurological events, or ensure that the hospital site will include safe use conditions necessary to mitigate the risks. Based on the incidence and serious risks of CRS, neurotoxicity, and the need to have tocilizumab on-site should CRS occur, a REMS that includes elements to assure safe use is necessary to ensure that the benefits of Yescarta outweigh the risks of CRS and neurotoxicity. The Applicant's proposed REMS comprised of only a communication plan will not be sufficient to mitigate such severe risks.

The following REMS proposal is the recommendation from DRISK. Please note that the final REMS and REMS materials must be commensurate with the serious risks in the final label.

8 DRISK Recommended REMS Requirements and Design

8.1.1 REMS Goals

The goals of the REMS should focus on the risks that the REMS is intended to mitigate and necessary to ensure the benefits outweigh the risks of the drug, as well as how the risks will be mitigated (ensuring that the drug is dispensed only in certain healthcare settings that are trained about the risks and that have a safe use condition; in this case patients treated with Yescarta must have access to tocilizumab to treat CRS). DRISK proposes the following goal and objectives for the Yescarta REMS:

- The goals of the Yescarta REMS Program are to mitigate the risk of cytokine release syndrome (CRS) and neurotoxicity by:
 - Ensuring that health care settings that administer Yescarta are specially certified and have on-site, immediate access to tocilizumab
 - Ensuring those who prescribe, dispense or administer Yescarta are trained about the about the management of cytokine release syndrome and neurotoxicity

8.1.2 REMS Requirements

During clinical trials, to mitigate the risks of CRS and neurotoxicity the Applicant provided training and education materials to relevant prescribers and hospital staff who would be involved in the administration and dispensing of Yescarta. If approved, in order to ensure that all hospitals are certified and staff are appropriately trained to manage these serious risks, DRISK recommends that certification be required as an ETASU in the REMS and are as follows:

- 1) Healthcare settings (hospitals) that dispense Yescarta must be certified, and
- 2) Yescarta must be dispensed to patients only in certain healthcare settings, specifically certified hospitals with on-site, immediate access to tocilizumab

Given that tocilizumab is used to manage the symptoms of CRS, and that it needs to be available on site and readily available within a narrow time frame should CRS occur, DRISK recommends Yescarta only be dispensed to patients with evidence or other documentation of safe-use conditions (immediate on site availability with a minimum of 2 doses of tocilizumab prior to Yescarta treatment). Education on how and when tocilizumab should be administered should be covered as part of the hospital certification and training.

As a condition of certification of the healthcare setting the hospital (hospital designee) must agree to oversee and implement prescriber and appropriate staff training prior to dispensing Yescarta.

DRISK recommends including an implementation system as an element of the REMS so the Applicant takes reasonable steps to monitor and evaluate implementation of the aforementioned ETASU by health care providers, pharmacists, and other parties in the health care system that are responsible prescribing and dispensing Yescarta.

Lastly, the Applicant must also include a timetable for submission of assessments. The minimum requirements for submission are 18 months, 3 years, and 7 years post approval, however for this REMS program with ETASU, DRISK recommends that assessments are submitted at 6 months, 12 months and annually thereafter from the initial date of the approval of the REMS. The Applicant's proposed REMS

Assessment Plan should be revised to assess implementation of the ETASU and safe use conditions as well as the outcomes for risks the a REMS is intended to mitigate.

Please see the attached draft proposed REMS document for further information on the ETASU and REMS Program requirements.

8.1.3 REMS Materials and Key Risk Messages

REMS materials are helpful in communicating and educating the applicable stakeholders on the key risk messages and safe use conditions in the REMS. These materials also must be commensurate with how the risks are described in labeling, but should also be written in a manner that gives clear, yet succinct risk messages and or direction to prescribers.

We anticipate that the Applicant will plan to do marketing of this product should it get approved, therefore, we do not believe that the REMS letters to healthcare providers, professional societies, or the REMS factsheet that was proposed as part of the CP are necessary. The Applicant may want to consider having a REMS website to house all of the REMS materials, particularly the Patient/Caregiver Wallet Card and the CRS algorithm for ease of access.

8.1.4 REMS Assessment Plan

Once an agreement is made on the necessary elements of the REMS, the Assessment Plan must be revised to permit an assessment of whether the REMS is mitigating the risks as intended.

9 Conclusion & Recommendations

Based on the magnitude and severity of the risks of CRS and neurotoxicity, DRISK does not agree with the Applicant's proposed REMS comprised of only a communication plan will not be sufficient to mitigate such serious risks.

We recommend a REMS with an ETASU comprising hospital certification and documentation of a safe use condition of having tocilizumab on site to mitigate the risk of CRS should this occur. We recommend that prescriber training and education on the symptoms and management of CRS and neurotoxicity occur under the hospital certification element (i.e., the hospital or hospital designee will be responsible for training and educating the appropriate prescribers that will dispense Yescarta).

The REMS document should be harmonized, to the extent possible, with the REMS document for tisagenlecleucel, a similar product with a similar risk profile to axicabtagene ciloleucel. If there are any questions on the DRISK proposed REMS document, or the REMS materials and REMS Assessment Plan that the Applicant will submit in the near future, please reach out to us directly.

10 References

¹ Howlader N, Noone A, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2013. National Cancer Institute Bethesda, MD, http://seercancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016. Accessed July 2017.

² Flowers CR, Sinha R, Vose JM. Improving outcomes for patients with diffuse large B-cell lymphoma. *CA: A Cancer Journal for Clinicians*. 2010;60(6):393-408.

³ Hitz F, Connors JM, Gascoyne RD, Hoskins P, Moccia A, Savage KJ, Sehn LH, Shenkier T, Klasa R. Outcome of Patients with Chemotherapy Refractory and Early Progressive Diffuse Large B Cell Lymphoma After R-CHOP Treatment. *Blood (ASH Annual Meeting Abstracts, Poster Session)*. 2010;116.

⁴ Crump M, Kuruvilla J, Couban S, MacDonald DA, Kukreti, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. *J Clin Oncol*. 2014;32(31):3490.

⁵ Yervoy REMS (subsequently released) available in released REMS data files at <https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm>.