Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	125646
PDUFA Goal Date	October 3, 2017
OSE RCM #	2017-592
Reviewer Name(s)	Naomi Redd, Pharm.D.
Team Leader	Elizabeth Everhart, MSN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	July 6, 2017
Subject	Consult review to the Center for Biologics Evaluation and Research on Applicant proposed REMS
Established Name	tisagenlecleucel
Trade Name	Kymriah
Name of Applicant	Novartis
Therapeutic Class	To be determined

Table of Contents

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 Novartis's proposed REMS comprised of a communication plan (CP) submitted for the new Biologics License Application (BLA 125646) tisagenlecleucel (Kymriah). 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 clinical trial, prior to initiating treatment, hospitals and prescribers were required to undergo certification and training to understand the risks and management of CRS and neurotoxicity. If Kymriah is approved, the Applicant's 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 review division does 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 to mitigate the risk of CRS. 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

The patient must receive lymphodepleting chemotherapy with cyclophosphamide and fludarabine, prior to receiving Kymriah. The patient's T cells are extracted by leukophoresis and then modified ex vivo using a lentiviral vector encoding an anti-CD19 chimeric antigen receptor to fuse with Kymriah. These modified cells are infused back into the patient's body, where they bind to the ALL cells and normal B cells to promote T-cell expansion, activation and target cell elimination.[1]

Kymriah is a CD19-directed genetically-modified autologous immunotherapy indicated in combination with lymphodepleting chemotherapy for the treatment of pediatric and young adult patients 3 to 23 years of age with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).[2] Kymriah is a single, one-time treatment with the proposed following dose:[a]

- For patients 50kg and below: IV infusion of $0.2 – 5.0 \times 10^6$ transduced viable T cells/kg of body weight
- For patients above 50kg: IV infusion of $0.1 – 2.5 \times 10^8$ transduced viable T cells

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

The intended setting in which the drug is likely to be administered is an inpatient hospital setting or infusion center. Kymriah was granted orphan drug designation on January 31, 2014 and Breakthrough Therapy Designation on April 7, 2016. The Applicant submitted the BLA application for Kymriah on February 2, 2017. The Prescription Drug User Fee Act (PDUFA) date is October 3, 2017. Kymriah is currently not marketed in any other jurisdiction.

1.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 125646 relevant to this review:

- 04/07/2016: Breakthrough Therapy Designation (BTD) granted
- 02/02/2017: BLA 125646 submission for tisagenlecleucel received
- 03/28/2017: Fast track designation granted
- 05/01/2017: Information Request (IR) sent to the Applicant based on DRISK Review of CP REMS. The Applicant was asked to submit education and training materials on the risks of Kymriah that were used in clinical trials.
- 07/12/2017: Oncologic Drug Advisory Committee meeting planned to discuss 1) post-marketing considerations for risk mitigation for short-term toxicities, particularly cytokine release syndrome, and 2) long-term follow-up for anticipated safety concerns related to the potential for insertional mutagenesis and secondary malignancies 3) whether the benefits justify the risks for a marketing approval of tisagenlecleucel for the proposed indication.

2 Therapeutic Context and Treatment Options

2.1 DESCRIPTION OF THE MEDICAL CONDITION

Acute lymphoblastic leukemia (ALL) is the most common malignancy diagnosed in children, representing one quarter of all pediatric cancers.[3,b] The majority of patients diagnosed with ALL are less than 19 years of age, and the peak age at initial diagnosis is between 2-6 years old.[1] Nearly 3,000 children are diagnosed with ALL in the Unites States each year. Cure rates approach 90% if the patient responds to initial therapy; however, prognosis is poor with each relapse.[c] There is between 100-200 cases per year of r/r ALL in the US, and treatment options become less effective with each relapse.[1]

2.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Treatment options for r/r ALL are minimal, and as mentioned above, these therapies become less effective with each relapse. Table 1 provides a summary of FDA Approved treatment options with a brief summary of efficacy, safety, and risk management of each drug.

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

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

Table 1: Summary of FDA Approved Treatment Options Relevant to Proposed Indication

Product Trade Name (Generic) **Year of Approval**	**Indication**	**Efficacy**[1]	**Important Safety and Tolerability Issues**	**Risk Management Approaches/Boxed Warning, Medication Guide**
Clolar[4] 2004	Pediatric patients 1 to 21 years old with r/r ALL after at least 2 prior regimens	CR: 11.5% DOR: 2.5 months	Myelosuppression (5.1); Tumor Lysis syndrome (5.4), Systemic Inflammatory Response Syndrome (5.5)	No Boxed Warnings or REMS
Marqibo[5] 2012	PH chromosome negative adult r/r ALL in second or greater regimens	CR: 15.4% (n=65; 45% under age 30) DOR: 2 months	Fatal if given IV (5.1); Neurologic toxicity (5.3), Tumor lysis syndrome (5.5)	Boxed Warning – must be given only IV
Blincyto[6] Accelerated approval 2014	PH chromosome negative r/r ALL with dosing in patients <45kg and >45kg	CR: 32.9% (n=23) Median DOR: 6 months (0.5-16.4)	CRS: any grade – 11%, ≥ Grade 3 – 4% Neurotoxicity: 64% Risk of "gasping syndrome" in pediatric patients due to Benzyl Alcohol preservative (5.12)	Boxed Warning – CRS & Neurotoxicity CP REMS; addresses the risk of CRS, neurotoxicity, and preparation/med errors
CR = complete response, DOR = duration of response				

3 Benefit Assessment

Kymriah efficacy was presented at CBER's Safety Working Group on June 8, 2017 by Dr. O'leary, the clinical reviewer for this application.[1] In the Applicant's Study B2202, 83 patients were enrolled and 63 patients were treated. Nearly 83% of patients (n=52) had a complete remission (CR), of these patients, 19% (n=12) had a complete remission with an incomplete hematologic recovery (CRi). Eleven patients (17.5%) had no response or an unknown outcome. The estimated event-free survival (EFS) at 6 months was 69.6% and at 12 months it was 53.3%. There have been 11 relapses in 52 responders to date, prior

to alternative therapy. The clinical reviewer stated that these results are statistically significant, and shows a clear benefit.[d] 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 neuropsychiatric events. In Study B2202 47% (n=32) of patients experienced severe/life threatening ≥ Grade 3 CRS. All patients that experienced ≥ Grade 3 CRS were admitted to the ICU. Symptoms of CRS included high fevers, hypotension, increased oxygen requirements/ventilator support, renal failure (6 patients required dialysis) and late CNS bleeds. The median time to onset was 3 days (range 1-22 days), with a median duration of 8 days (1-36 days). It appeared that patients who had bulky disease, high IL-6 and C-reactive protein levels had the highest risk of experiencing CRS. There were no fatal events from CRS reported. The majority of patients (49%; n = 26) who experienced CRS where treated with tocilizumab, followed by corticosteroids (26%; n= 14), and siltuximab (9%; n=5).

Transient neuropsychiatric events occurred in 44% (n=30) of patients; 15% (n=10) were classified as a Grade 3 event. There were no cases of cerebral edema. The majority of neurological events appeared to occur during CRS. Twelve events in 6 patients occurred after the resolution of CRS, and included encephalopathy, amnesia, tremors, lethargy, agitation, confusions, delirium, dysphagia, and dysarthria. Treatment of neurological events is confined to seizure prophylaxis, and the use of corticosteroids when necessary.

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 Kymriah.

5 Expected Postmarket Use

Kymriah is expected to only be dispensed at an inpatient hospital or infusion center. The patient must receive a lymphodepleting chemotherapy prior to receiving the Kymriah infusion. Patients were given fludarabine and cyclophosphamide as the lymphodepleting chemotherapy regimen. Kymriah is prepared from autologous blood of the patient. The patient's T cells were collected by leukapheresis and then shipped to Novartis Morris Plains facility to complete the autologous conversion of the patient's T cells with Kymriah, which were then shipped back to the hospital or infusion center for the patient to receive the final drug product. Per the Applicant's protocol, the infusions took approximately 6 hours, and patients were advised to stay in the infusion center for at least 2 hours after the infusion was complete, and to stay within a 2 hour drive radius of the hospital/infusion site for 4 weeks after the infusion was completed.

[d] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

5.1 HEALTHCARE SETTING

The Applicant states that the leukapheresis collection sites must be FDA-registered 21CFR1271 tissue establishments, and Foundation for Accreditation of Cellular Therapy (FACT) accredited. The Applicant states that they will maintain a Chain of Identity from apheresis pick-up at the apheresis site through manufacturing at the Novartis Morris Plains facility, and delivery back to the hospital or infusion center to mitigate risk of medication errors or getting the drug to the wrong patient.

The Applicant plans to continue training and certifying hospitals to be able to prescribe and administer Kymriah. During the clinical trial, training included education on the risks and management of CRS and neurotoxicity. In the Applicant's Pharmacovigilance Plan, they maintain that they will train and certify the leukapheresis and cryopreservation facilities for the safe and effective collection cells, and will train and certify hospitals to be able to prescribe and administer Kymriah. The Applicant states that training will focus on appropriate patients as per FDA approved indication, US Prescribing Information, safety management of adverse events (specifically CRS, neurological/psychiatric events and other AEs), process and patient management, chain of identity, and a REMS. The REMS that the Applicant proposes is a CP, with materials educating healthcare providers and professional societies on the risk of CRS and neurotoxic events, including a CRS Management Algorithm and a Patient/Caregiver Wallet Card recognizing the events of CRS and neurotoxicity and when to go for treatment for the management of these events.

6 Risk Management Activities Proposed by the Applicant

6.1 REVIEW OF APPLICANT'S PROPOSED REMS

The applicant submitted a proposed REMS with their BLA application. The REMS consists of a CP that includes a REMS Letter for healthcare providers (HCPs), REMS Factsheet, CRS Management Algorithm, Patient/Caregiver Wallet Card, REMS Letter for Professional Societies, and a REMS Website. The Applicant states in their REMS Supporting Document that the REMS can be approved without elements to assure safe use (ETASU) and an implementation system. In the IND Novartis determined that additional certification and training was necessary to support hospitals and prescribers who administer Kymriah and mitigate the risk of CRS and neurotoxicity. They did not provide a rationale as to why this product can be approved **without** an ETASU and an implementation system.

The Applicant's REMS submission included a REMS Document and a REMS Supporting Document. The submission was missing the following materials:

- REMS Letters to Healthcare Providers
- REMS Letter to Professional Societies
- REMS Factsheet
- CRS Management Algorithm
- Patient/Caregiver Wallet Card
- Landing page of REMS Website

DRISK considers this an incomplete REMS submission.

6.1.1 REMS Goals

The Applicant's goal of the Kymriah REMS is to educate HCPs about the serious risks of CRS, and neurological and psychiatric events by:

- Informing HCPs about the risk of CRS which may be life-threatening and occurred in patients receiving Kymriah
- Informing HCPs about the serious clinical manifestations associated with CRS
- Informing HCPs about the serious risk of neurological and psychiatric events observed with Kymriah treatment
- Informing HCPs of the timing of CRS, and neurological and psychiatric events observed in relation to the Kymriah infusion
- Informing HCPs about management of CRS
- Informing HCPs to educate patients and their caregivers about the signs and symptoms of CRS, and neurological and psychiatric events, and when to seek immediate medical attention

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. Of note, these materials were not included in their submission.

REMS Letter for HCPs

As per the REMS Supporting Document, the proposed *REMS Letter for HCPs* 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 risks of neurological and psychiatric events that have been observed with Kymriah treatment.

REMS Factsheet

As per the REMS Supporting Document, the REMS Factsheet would expand on the same safety information in the REMS Letter for HCPs. The REMS Factsheet would instruct HCPs to reference additional REMS tools including the CRS Management Algorithm and the Patient/Caregiver Wallet Card.

CRS Management Algorithm

As per the REMS Supporting Document, the algorithm for the treatment of CRS as found in the Prescribing Information (PI) will be made available to HCPs as a laminated card.

Patient/Caregiver Wallet Card

As per the REMS Supporting Document, the wallet card would provide information to patients/caregivers on the signs and symptoms of CRS, and neurological and psychiatric events that require immediate medical attention.

REMS Letter for Professional Societies

The REMS Letter for Professional Societies was not included in the submission. As per the REMS Supporting Document, the *REMS Letter for Professional Societies* will outline the identical information listed above in the *REMS Letter for HCPs.*

REMS Website

The website landing page was not included in the submission. As per the REMS Supporting Document, the Kymriah REMS Program Website [www.Kymriah-rems.com] will include serve as a place to house the REMS materials (PI, Medication Guide, letters, REMS Factsheet, CRS Management Algorithm, and Patient/Caregiver Wallet Card.

6.1.3 REMS Assessment Plan

The Applicant's proposed t REMS Assessment Plan includes an assessment of the metrics of the number and to whom the materials were distributed as well as knowledge, attitudes, and behavior surveys of HCPs.

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

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

7.0 DISCUSSION

The review of this application is ongoing however, the clinical reviewer preliminary analysis is that the efficacy is compelling for providing a clear benefit for pediatric patients with r/r ALL. However should this application be approved, the clinical review team and this reviewer recommends 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, a factsheet, a CRS management algorithm, and distribution of a patient/caregiver wallet card. . In general, the Applicant has proposed a REMS that is similar to the Blincyto (blinatumomab) REMS.[7] Blincyto was approved under accelerated approval with a REMS comprised of a communication plan for the treatment of PH chromosome negative r/r ALL. CRS and neurotoxicity are included as box warnings in the Blincyto product labeling. For Blincyto, any grade of CRS occurred in 13% of patients greater than or equal to 45 kg and, 11% of those less than 45 kg. The first cycle of Blincyto is provided as continuous

infusion for 28 days. Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle. The incidence of CRS reported in tisagenlecleucel trials is considerably higher with 47 **%** of the patients in the tisagenlecleucel pivotal study B2202 experienced grade 3 or greater CRS.

This REMS proposal differs significantly from the Applicant's risk mitigation strategies that occurred during the product's clinical trial. Prior to dispensing Kymriah, the Applicant required treatment sites to undergo training and education programs for the proper collection of cells, proper patient dispensing, as well as education and training on CRS, neurotoxicity, and other adverse events that may occur as a result of Kymriah administration. The Applicant provided training and educational materials on the symptomology and management of adverse events, specifically CRS, and prescribers had to complete a "knowledge check" upon viewing this information prior to dispensing Kymriah.

The Applicant is voluntarily proposing to continue training and educating treatment sites and prescribers but not as part of a REMS. If Kymriah is approved, voluntary training may not ensure that that all applicable stakeholders are trained, that treatment sites have policies and procedures in place, or that safe use conditions (i.e., immediate on site availability of tocilizumab) are met prior to treating a patient.

In the Kymriah clinical trials, hospitals and prescribers were required to undergo training to understand the risks and management of CRS and neurotoxicity. A CP REMS does not ensure that prescribers and hospital will undergo the appropriate training to mitigate these risks, 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 are necessary to ensure that the benefits of Kymriah 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 serious 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.

8.1 DRISK RECOMMENDED REMS REQUIREMENTS AND DESIGN

8.1.1 REMS Goals

The goals of the REMS goals 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 access to tocilizumab to treat CRS). DRISK proposes the following goal and objectives for the Kymriah REMS:

- The goal of the Kymriah REMS Program is to mitigate the risk of cytokine release syndrome (CRS) and neurological and psychiatric events by:

- Ensuring Kymriah is dispensed only in certified hospitals and clinics that have on-site immediate access to tocilizumab

- Ensuring those who prescribe, dispense or administer Kymriah are trained about the role of tocilizumab to treat CRS

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 Kymriah. 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) Health care settings (hospitals) that dispense Kymriah are specially certified, and
2) Kymriah is only dispensed to patients with evidence or other documentation of safe-use conditions (immediate on site availability of a minimum of 2 doses of tocilizumab prior to treatment).

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 Kymriah only be dispensed to patients with evidence or other documentation of safe-use conditions to mitigate this risk (immediate on site availability with a minimum of 2 doses of tocilizumab prior to Kymriah 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 Kymriah.

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 Kymriah.

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

The Applicant provided only an outline of the minimum requirements that must be assessed in a REMS. Once and agreement is made on the necessary elements of the REMS, the Assessment Plan must revised to better determined how the pertinent risks of the REMS will be assessed.

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 of 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 Kymriah). 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] Safety Working Group Clinical Presentation for Tisagenlecleucel, M. O'leary, MD, Clinical Reviewer, June 8, 2017

[2] Draft Kymriah Label, May 26, 2017

[3] Kanwar V. Pediatric Acute Lymphoblastic Leukemia. January 31, 2017 Emedicine.medscape.com/article/990113 accessed June 13, 2017

[4] Clolar U.S. Prescribing Information, Sanofi US, Revised October 2016

[5] Marqibo U.S. Prescribing Information, Spectrum Pharmaceuticals, Revised July 2015

[6] Blincyto U.S. Prescribing Information, Amgen, Revised May 2017

[7] Blincyto REMS https://www.accessdata.fda.gov revised January 30, 2017

4 Pages determined to be not relesable: (b)(4);(b)(5)