Division of Risk Management (DRM)
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	125703
PDUFA Goal Date	August 10, 2020
OSE RCM #	2020-405
Reviewer Name(s)	Brad Moriyama, Pharm.D. Suzanne Robottom, Pharm.D.
Team Leader	Naomi Boston, Pharm.D. Shelly Harris, ScD, MPH
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	July 23, 2020
Subject	REMS consult
Established Name	Brexucabtagene autoleucel
Trade Name	Tecartus
Name of Applicant	Kite Pharma, Inc.
Therapeutic Class	CD19-directed genetically modified autologous T cell immunotherapy
Formulation(s)	Chimeric antigen receptor (CAR)-positive T cells suspension, approximately 68 mL in single infusion bag
Dosing Regimen	2×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 CAR-positive viable T cells

1 Introduction

This review is in response to a consult from Center for Biologics Evaluation and Research (CBER) to evaluate the risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Tecartus (brexucabtagene autoleucel). Kite Pharma, Inc. submitted a Biologic Licensing Application (BLA) 125703 for brexucabtagene autoleucel with the proposed indication for the treatment of adult patients with relapsed or refractory mantle cell lymphoma.[1] This application is under review in CBER. The applicant proposed a combined REMS with Tecartus and the approved CD19-directed genetically modified autologous T cell immunotherapy Yescarta (axicabtagene ciloleucel). Tecartus and Yescarta share the same risks of cytokine release syndrome (CRS) and neurological toxicities and the REMS requirements will be the same to mitigate these risks. The REMS for Yescarta was originally approved on October 18, 2017, to ensure the benefits of the drug outweigh the risks of CRS and neurological toxicities. The proposed combined Yescarta and Tecartus REMS consists of an elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

2 Background

2.1 Product Information

Tecartus (brexucabtagene autoleucel), a NME, is a CD19-directed genetically modified autologous T cell immunotherapy, proposed for the treatment of adult patients with relapsed or refractory mantle cell lymphoma. Brexucabtagene autoleucel is supplied as a chimeric antigen receptor (CAR)-positive T cells suspension, approximately 68 mL in a single infusion bag. The proposed dosing regimen is 2×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 CAR-positive viable T cells. Brexucabtagene autoleucel is not currently approved in any jurisdiction. Brexucabtagene autoleucel was designated as orphan designation and breakthrough therapy. If approved, the indication will be approved under accelerated approval based on overall response rate and durability of response.

The proposed label for brexucabtagene autoleucel has a boxed warning for cytokine release syndrome and neurologic toxicities. The other serious risks associated with brexucabtagene autoleucel in the proposed label include hypersensitivity reactions, severe infections, prolonged cytopenias, hypogammaglobulinemia, secondary malignancies, and effects on ability to drive and use machines.

2.2 Regulatory History

The following is a summary of the regulatory history for brexucabtagene autoleucel BLA 125703 relevant to this consult:

- 4/4/2016: Orphan designation granted
- 6/15/2018: Breakthrough therapy designation granted
- 9/19/2019: In the Pre-BLA preliminary meeting responses, the Applicant asked “Does the Agency agree with a combined REMS program for KTE-X19 and Yescarta?” The Agency stated that the approach appears reasonable assuming the safety profile of KTE-X19 is similar to Yescarta. The Agency requested in the BLA submission of the proposed REM include

information regarding existing Yescarta sites that would transition to a combined REMS and "receive appropriate education" and provide details on education in the transition plan, provide details on administering and tracking of knowledge assessments at certified sites and details of the learning management system utilized, and provide a detailed assessment plan and timetable for submission of the combined assessments including: a 6-month assessment to assess site certification under the combined REMS and a 12-month assessment to assess whether the combined REMS is meeting its goals.

- 12/11/2019: BLA 125703 submission for the treatment of adult patients with relapsed or refractory mantle cell lymphoma received
- 3/26/2020: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that the proposed combined REMS program for Tecartus and Yescarta is under review and there will be communication regarding the details of the REMS program at a later date.
- 7/17/2020: CBER contacted DRM via email and is seeking feedback on the additional metrics in the assessment plan.

3 Review of Applicant's Proposed REMS

The Applicant proposed a combined REMS for Yescarta and Tecartus. The proposed combined REMS consists of an ETASU that requires certification of hospitals and their associated clinics must become certified in the Yescarta and Tecartus REMS in order to dispense Yescarta and Tecartus. Before infusing Yescarta or Tecartus staff at the certified hospital or associated clinic must verify that a minimum of two doses of tocilizumab are on-site for each patient and are available for immediate administration (within 2 hours) for the management of cytokine release syndrome. The REMS also includes an implementation system and a timetable for submission of assessments.

The Yescarta REMS will need to be modified to align with the combined REMS for Yescarta and Tecartus. This modification is currently under review by CBER.

DRM agrees that parallel, complete submissions need to be submitted to both applications simultaneously. DRM provided this comment to CBER on May 4, 2020 on submission of modifications to the proposed REMS documents and REMS materials for the combined Yescarta and Tecartus REMS.

3.1 REMS DOCUMENT

In general, DRM reviewers agreed with the Applicant's proposed REMS; however additional changes were needed to the REMS Document. The following comments were provided in track changes to CBER via email on June 5, 2020 on the proposed REMS Document submitted on 12/11/2019.

- Change the name of the REMS from "Kite ONC" REMS Program" to "YESCARTA (axicabtagene ciloleucel) and TECARTUS (brexucabtagene autoleucel)" REMS Program

- Delete the following sentence: "The Kite ONC REMS (KOR) Program currently includes two anti-CD19 Chimeric Antigen Receptor (CAR) T-cell therapies YESCARTA® (axicabtagene ciloleucel) and KTE-X19 [TRADENAME]"

- Replace "a Kite Chimeric Antigen Receptor (CAR) T-cell therapy" with "YESCARTA and TECARTUS" throughout the REMS document

- CBER commented about the address of the REMS Program website, specifically if the Applicant must have a new domain name for the Yescarta REMS after the approval of the combined Yescarta and Tecartus REMS. DRM stated that the applicant may continue to use the Yescarta REMS website (www.yescartaREMS.com) as an active domain.

- DRM provided the following recommendations for changes to the REMS document based on feedback during the review by ORP and OCC. DRM recommends removing language from the following sections of the REMS Document:

    - In the section "To support REMS Program operations, Kite Pharma, Inc. must:

        5. Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the REMS program ~~hospitals and their associated clinics that are certified to administer a Kite CAR T therapy in the Kite ONC REMS Program.~~

    - In the section "To ensure REMS participants' compliance with the REMS Program, Kite Pharma, Inc. must:"

        12. Audit all certified hospitals within 180 calendar days ~~after product delivery~~ of the first order for the first patient for YESCARTA and TECARTUS ~~a Kite CAR T therapy~~ to ensure that all processes and procedures are in place and functioning to support the requirements of the YESCARTA and TECARTUS ~~Kite ONC~~ REMS Program. Certified hospitals and their associated clinics must also be included in the Kite Pharma, Inc. ongoing annual audit plan.

DRM provided the following comment to CBER on June 4, 2020 regarding the use of REMS participants on the proposed Yescarta and Tecartus REMS Document.

- CBER commented that "The Kymriah REMS Document uses the language, requiring them to "*Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the REMS Program*" while the language in the Yescarta REMS Document states "*Establish and maintain a validated, secure database of hospitals and their associated clinics that are certified to administer Yescarta in the YESCARTA REMS Program."* We would like for the Tecartus and Yescarta REMS Document to use similar language regarding "REMS participants" (which will be in alignment with Kymriah, and also the new CAR-T, Breyanzi, and the REMS Guidance [https://www.fda.gov/media/77846/download]. From the Guidance, it was our understanding that "REMS participants" is a broader term, and includes certified hospital settings and also HCPs who prescribe/dispense/administer the product."

- DRM agrees with the edit to revise to "REMS participants" as it is more consistent with the REMS template and it is a broader term.

CBER requested feedback on the Applicant's Learning Management System (LMS), and whether it needed to be specifically documented in the REMS or as a separate material. The LMS that the Applicant proposed is a system in which the training and knowledge assessment on the REMS will occur. DRM provided comments to CBER on June 4, 2020 on the LMS. In general, the feedback to CBER regarding this LMS was that this system is already covered under training that is made available online, and therefore does not need to be called out in the REMS document, nor does it need to be made available as a separate training. There are no previous precedents in calling out a learning management system in the REMS document.

To support REMS Program operations, Kite Pharma, Inc. must:

2. Establish and maintain a REMS Program website (www.KiteONCREMS.com). The REMS Program website must include the capability to complete training online, maintain records of that training, and the option to print the Prescribing Information, Medication Guide, and REMS materials. The product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Program website.

3.2 REMS MATERIALS

DRM provided the following comment to CBER on May 4, 2020 on the proposed Training Slide Deck submitted on 12/11/2019.

- DRM agrees with removing the indication information, as it is not necessary to support the risk mitigation strategies.

DRM provided the following comments in track changes to CBER on June 5, 2020 on the proposed Hospital Enrollment Form submitted on 12/11/2019.

- Change name of the REMS from "Kite ONC" REMS Program" to "YESCARTA and TECARTUS" REMS Program
- Replace KTE-X19 [TRADENAME] with TECARTUS
- The email address KiteONCREMS@kitepharma.com needs a new name.
- In the section Kite ONC REMS Hospital Attestations, as a condition of certification, the certified hospital and its associated clinics must: "Report suspected serious adverse events associated with a Kite CAR T therapy (either YESCARTA or KTE-X19 [TRADENAME]) by contacting Kite at 1-844-454-KITE or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch." DRM recommended deleting this sentence. This is not a requirement in the REMS Program. We also noted that this language is in the currently approved Hospital Enrollment Form for Yescarta.

- Replace “Kite CAR T therapy” with “YESCARTA or TECARTUS”

- In the section Kite ONC REMS Hospital Attestations, as a condition of certification, the certified hospital and its associated clinics must: DRM recommended adding the following sentence: “Provide the patient with the Patient Wallet Card.”

- In the section Kite ONC REMS Authorized Representative Attestations: DRM recommended the following revision as it is not part of the REMS requirements (This is in the currently approved Hospital Enrollment Form for Yescarta): Prior to discharge, provide patients/caregivers with the Patient Wallet Card ~~and instruct patient to remain within close proximity (within 2 hours) of the certified administering hospital and its associated clinics for at least 4 weeks following YESCARTA or KTE-X19 [TRADENAME] infusion.~~

3.3 REMS ASSESSMENT PLAN

DRM reviewed the proposed assessment plan for Yescarta and Tecartus REMS. We have the following recommendations for incorporation in either the current assessment plan at approval or in future assessment plan revisions.

- We recommend that the assessment plan metrics align with the draft guidance “REMS Assessment: Planning and Reporting”. The sponsor should be referred to the guidance for assessment plan development.
- We agree with the highlighted proposed metrics.
- For the metric, “List of hospitals certified under the YESCARTA REMS that did not transition to the YESCARTA and TECARTUS REMS by 90 days from TECARTUS approval”, consider if you would like to collect the reasons why the hospitals did not transition to the new REMS.
- Refer to the draft guidance. Consider the inclusion of any metrics related to “Safe Use Behaviors” or “Health Outcomes”, if these metrics are warranted.
- Consider if you want the sponsor to submit an updated audit plan and non-compliance plan at least 90 days after approval. This audit plan should include definitions for minor, major, and critical deviations. The non-compliance plan should include criteria for decertification and subsequent recertification and examples of what would be considered “critical non-compliance findings”
- Additional audit and non-compliance metrics to consider include:
    i. The number of audits expected, and the number of audits performed
    ii. The number and type of deficiencies noted for each group of audited stakeholders
    iii. A summary report of non-compliance, associated corrective and preventive actions (CAPA) plans, and the status of CAPA plans, including but not limited to:
        1. A copy of the Non-Compliance Plan which addresses the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each event, and under what circumstances a stakeholder would be suspended or de-certified from the REMS
            a) For those with deficiencies noted, report the number that successfully completed a corrective and preventative action (CAPA) plan within the timeframes specified in the audit plan

b) For any that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken

2. The number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of noncompliance, report the following information:
    a) The unique ID(s) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time
    b) The source of the noncompliance data
    c) The results of root cause analysis
    d) What action(s) were taken in response

iv. Confirmation of documentation of completion of training for relevant staff

v. A comparison of the findings to findings of previous audits and an assessment of whether any trends are observed

4 Conclusion

DRM reviewed the proposed combined REMS for Yescarta and Tecartus per the consult request from CBER. Our comments to CBER are summarized in Section 3 of this consult review.

DRM agrees a combined REMS is appropriate as both Yescarta and Tecartus share the same risks of CRS and neurological toxicities and require the same risk mitigation strategies and training to mitigate these risks**.**

The Yescarta REMS will need to be modified to align with the combined REMS for Yescarta and Tecartus. This modification is currently under review by CBER.

We have no additional comments on the proposed combined REMS for Yescarta and Tecartus.

5 Appendices

5.1 REFERENCES

[1] Proposed prescribing information for brexucabtagene autoleucel as currently edited by FDA, July 10, 2020.