Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Consult Review - ADDENDUM

Date:	August 24, 2017
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Subject:	Review of the amended proposed REMS August 7, 2017 and August 18, 2017
Drug Name(s):	tisagenlecleucel (Kymriah)
Therapeutic Class:	TBD
Application Type/Number:	BLA 125646
Applicant/sponsor:	Novartis
OSE RCM #:	2017-592

APPROVED
By Naomi Redd, Pharm.D. at 10:13 am, Aug 28, 2017

APPROVED
By Cynthia LaCivita at 3:53 pm, Aug 28, 2017

1 INTRODUCTION

This review provides comments to the Center for Biologics Evaluation and Research (CBER) on the amended proposed risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) for tisagenlecleucel submitted on August 7, 2017 and August 18, 2017. Novartis is seeking approval for tisagenlecleucel 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). The PDUFA date for this Application is October 3, 2017.

2 MATERIALS REVIEWED

- Novartis' proposed amended REMS with ETASU submitted to CBER August 7 and August 18, 2017
- Draft of near final label August 23, 2017

Previous DRISK consult reviews related to the original submission

- Redd N. DRISK REMS Consult Review for proposed REMS for tisagenlecleucel BLA 125646; July 7, 2017

3 RESULTS OF REVIEW

Novartis accepted the revisions received from the Agency on August 3, 2017, which included substantial edits to their proposed REMS goals, ETASU and implementation system. General comments were also given to CBER on the Applicant's REMS materials since labeling was still ongoing at that time. This proposal was resubmitted on August 7, 2017 without the REMS materials. Additionally, the Applicant's proposed Assessment Plan was incomplete. DRISK provided comments to CBER in on the Applicant's REMS document (clarification on language in the Applicant's implementation plan), and an example of language to be included for the REMS Assessment Plan in the REMS Supporting Document. CBER sent these comments to the Applicant on August 16, 2017, and the Applicant responded with their final proposed REMS, REMS Supporting Document and REMS materials on August 18, 2017.

DRISK has the following comments for CBER to relay to Novartis on their final proposed submission:

- **REMS Document -** minor edits were made to the REMS document (addition of necessary punctuation, spacing and corrective spelling), and the clarification that the Kymriah REMS Live Training Slides were added to the materials.
- **REMS Supporting Document –** edits were made to be consistent with the REMS document.
- **REMS materials -** materials reviewed included the training program slides, knowledge assessment, hospital enrollment form, patient/caregiver wallet card, and the landing page of the REMS website. The following recommendations for CBER to relay to Novartis are to improve readability which will in turn augment the communication of the risk messages of the REMS.

- **HCP Training Slides:** No comments for Novartis.

- **Hospital Enrollment Form:** We recommend removing some content that is not necessary on the form about REMS goals, as well highlighting the information about how to return the form. These changes will allow the form to be less cluttered and improve readability.

- **Patient /Caregiver Wallet Card:** We have made substantial recommendations to the Patient/Caregiver Wallet Card. In an effort to keep the revisions clear, we have completely deleted some text, instead of putting a red line through it. In addition, our added text may not always be noted as new, in order to show you what the layout of the card would look like. The patient information should be clearly laid out with a heading that identifies the information as such. Include a heading that says "Patient Information" on the back of the card. The signs and symptoms listed should only be the ones that are severe and life-threatening, per the Medication Guide. Delete the additional signs and symptoms. There also needs to be a statement that identifies these signs and symptoms as severe and life threatening. Increase the font size of the action statement in red for the patients. The message for patients to stay within 2 hours of a Kymriah treatment site for at least 3-4 weeks should also be moved to be with other messaging that is for the patient.

  The Healthcare Provider side of the card needs to be reorganized. The risk information on CRS should be upfront. The indication can be moved down below the fold of the card. The following statement is for the patient and can be removed from the HCP side of the card, "Patients and their caregivers should plan to say within 2 hours of a Kymriah treatment side for at least 3 to 4 weeks after receiving Kymriah treatment, unless otherwise indicated by the doctor." Include an exclamation point or similar graphic next to the CRS risk information to indicate this is important information. In focus group testing with emergency personnel, participants have stated that symbols like these that are common in emergency department settings, indicate important information that can be located quickly.

- **REMS Website:** Remove the two references to the stand along Kymriah REMS CRS Management Algorithm CRS algorithm at the bottom of the landing page since these pieces are not part of the REMS.

We also recommend that all REMS and REMS materials be consistent with final, approved FDA labeling.

4 CONCLUSION AND RECOMMENDATIONS

Provided that the Applicant makes the recommended edits, DRISK has no further recommendations to CBER on the Applicant's proposed REMS and REMS materials at this time.