

**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)**

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<b>Application Type</b>	BLA
<b>Application Number</b>	125746
<b>PDUFA Goal Date</b>	November 29, 2021
<b>OSE RCM #</b>	2021-834
<b>Reviewer Name(s)</b>	Brad Moriyama, Pharm.D., BCCCP Kate Oswell, M.A. Suzanne Robottom, Pharm.D.
<b>Deputy Division Director</b>	Doris Auth, Pharm.D.
<b>Review Completion Date</b>	October 12, 2021
<b>Subject</b>	REMS consult
<b>Established Name</b>	Ciltacabtagene autoleucel
<b>Trade Name</b>	Carvykti
<b>Name of Applicant</b>	Janssen Biotech, Inc.
<b>Therapeutic Class</b>	B cell maturation antigen (BCMA)-directed genetically modified autologous T-cell immunotherapy
<b>Formulation(s)</b>	Chimeric antigen receptor (CAR)-positive viable T cells suspension, in 30 mL or 70 mL patient specific infusion bag
<b>Dosing Regimen</b>	0.5 to $1 \times 10^6$ CAR-positive viable T-cells per kg of body weight, with a maximum dose of $1 \times 10^8$ CAR-positive viable T-cells per single infusion

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## 1 Introduction

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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) Document and REMS materials for the new molecular entity (NME) Carvykti (ciltacabtagene autoleucel). Janssen Biotech, Inc. submitted a Biologic Licensing Application (BLA) 125746 for ciltacabtagene autoleucel with the proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma after (b) (4) [REDACTED], including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody.<sup>1</sup> This application is under review in CBER. The applicant proposed a REMS with Carvykti. Carvykti shares the same risks of cytokine release syndrome (CRS) and neurological toxicities with the approved B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy Abecma (idecabtagene vicleucel). The REMS for Abecma was originally approved on March 26, 2021, to ensure the benefits of the drug outweigh the risks of CRS and neurologic toxicities. The proposed Carvykti REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

## 2 Background

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### 2.1 PRODUCT INFORMATION

Carvykti (ciltacabtagene autoleucel), an NME, is a BCMA-directed genetically modified autologous T-cell immunotherapy, proposed for the treatment of adult patients with relapsed or refractory multiple myeloma after (b) (4) [REDACTED], including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody. Ciltacabtagene autoleucel is supplied as a chimeric antigen receptor (CAR)-positive viable T cells suspension, in 30 mL or 70 mL patient specific infusion bag. The proposed dosing regimen is 0.5 to 1 × 10<sup>6</sup> CAR-positive viable T-cells per kg of body weight, with a maximum dose of 1 × 10<sup>8</sup> CAR-positive viable T-cells per single infusion. Ciltacabtagene autoleucel is not currently approved in any jurisdiction. Ciltacabtagene autoleucel was designated as orphan designation and breakthrough therapy.

The proposed label for ciltacabtagene autoleucel has a boxed warning for cytokine release syndrome, neurologic toxicities, hemophagocytic lymphohistiocytosis/macrophage activation syndrome, and prolonged and recurrent cytopenia. The boxed warning also states an early or delayed onset neurologic toxicity with some features of Parkinson disease distinct from typical neurologic toxicities associated with immune effector cell therapy, including irreversible, fatal or life-threatening toxicity, occurred following treatment with Carvykti. The other serious risks associated with ciltacabtagene autoleucel in the proposed label include serious infections including febrile neutropenia, hypogammaglobulinemia, hypersensitivity reactions, effects on ability to drive and use machinery, secondary malignancies, and blood, organ, tissue, and cell donation.

### 2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for ciltacabtagene autoleucel BLA 125746 relevant to this consult:

- 2/1/2019: Orphan designation granted
- 12/6/2019: Breakthrough therapy designation granted
- 3/31/2021: BLA 125746 submission for the treatment of adult patients with relapsed or refractory multiple myeloma, who previously received a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody received
- 7/29/2021: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that the proposed REMS program for Carvykti is under review and there will be communication regarding the details of the REMS program at a later date.

### **3 Review of Applicant's Proposed REMS**

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The Applicant proposed a REMS for Carvykti. The proposed REMS consists of an ETASU that requires certification of hospitals and their associated clinics in the Carvykti REMS to dispense Carvykti. Before infusing Carvykti, 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.

#### **3.1 REMS DOCUMENT**

In general, DRM reviewers agreed with the Applicant's proposed REMS; however additional changes were needed to the REMS Document. Edits to formatting and consistency with the template were provided in track changes to CBER via email on July 22, 2021 on the proposed REMS Document submitted on 3/31/2021. See the appendix for DRM edits to the proposed REMS Document. Minor edits were also provided in track changes to CBER via email on August 23, 2021.

Comments were provided in track changes to CBER via email on August 5, 2021 on the sponsor's comments in the proposed REMS Document. See appendix for DRM comments to the proposed REMS Document.

DRM provided the following comments to CBER via email on October 1, 2021 regarding the timing of providing the patient wallet card and verifying tocilizumab is available on-site in the proposed REMS Document.

- The Applicant intended to change the timing category for providing the Patient Wallet Card to "at discharge." However, when that change was made, the timing to "verify that a minimum of two doses of tocilizumab are available onsite....as a requirement of the REMS Program" was revised to "at discharge" as well. DRM believes that the Carvykti REMS should mimic the Kymriah REMS as follows:

<b>Before infusion</b>	<ul style="list-style-type: none"> <li>Verify that a minimum of two doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours) through the processes and procedures established as a requirement of the REMS Program.</li> </ul>
<b>Before discharge</b>	<ul style="list-style-type: none"> <li>Provide the patient with the Patient Wallet Card through the processes and procedures established as a requirement of the REMS Program.</li> </ul>

### 3.2 REMS MATERIALS

DRM provided the following comments to CBER via email on September 29, 2021 on the proposed REMS materials submitted on 3/31/2021.

#### Overall Comments:

- We note that your proposed labeling is currently being reviewed by the FDA. All REMS communication materials must be revised to be consistent with the final FDA approved labeling and resubmitted for review.
- All REMS program information must reflect what is in the REMS Document. Make any changes in the materials to be included in your next submission. This includes aligning the names of the REMS materials with the names of the materials in the REMS Document and the attestations that appear on the Hospital Enrollment Form.
- Phone numbers used by the CARVYKTI REMS may not link to information that is promotional in tone.

#### Healthcare Facility Enrollment Form (to become the Hospital Enrollment Form)

- Attestations on the form must align with the REMS Document.
- Bold the names of the following documents for ease of reading the attestations: Training Program, Knowledge Assessment, Patient Wallet Card
- The following attestation does not appear in the REMS document and should be removed: Performing re-education of all staff involved in the prescribing, dispensing, or administering of CARVYKTI if CARVYKTI has not been infused at least once within the first year from the date of certification of the Healthcare Facility in the CARVYKTI REMS.

#### Training Module (to become Training Program)

- The CRS Management Guide, Table 1: Cytokine Release Syndrome Management Algorithm on slide 17 is not easy to read, as it is in very small font. We recommend this chart be broken up into two slides so the font size may be increased, and participants can more easily read the content.

#### Patient Guide (if CBER/Sponsor does not accept recommendation to remove Guide)

- Having a navy only color scheme for the headings and content that are in close proximity to each other does not allow the reader to distinguish the two. Include more space between the heading questions and the content below or consider using a different font color for the headings.

- The content in light blue “For patients and healthcare professionals” and “Travel Advisory” on the right side of the pages does not stand out as it is intended to, due to the light font color and small font size. Consider putting the graphic and title in orange font and increasing the font size to stand out.

### **3.3 REMS ASSESSMENT PLAN**

If changes to the REMS assessment plan are necessary they will be communicated in a separate review.

## **4 Conclusion**

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DRM reviewed the proposed REMS Document and REMS materials for Carvykti per the consult request from CBER. Our comments to CBER are summarized in Section 3 and the appendix of this consult review. We have no additional comments on the proposed REMS for Carvykti.

## **5 Appendices**

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### **5.1 REFERENCES**

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<sup>1</sup> Proposed prescribing information for ciltacabtagene autoleucel as currently edited by FDA, October 4, 2021.