

**Department of Health and Human Services
Food and Drug Administration (FDA)
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Epidemiology (OBE)
Division of Epidemiology (DE)**

ADDENDUM TO PHARMACOVIGILANCE PLAN REVIEW MEMORANDUM

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To: Zhaohui Ye
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Subject: Addendum to Review of Pharmacovigilance Plan

Sponsor: Janssen Biotech

Product: CARVYKTI® (ciltacabtagene autoleucel)

BLA Number: STN 125746/0

Proposed Indication: Relapsed or refractory multiple myeloma

Submission Date: December 18, 2020

Action Due Date: February 28, 2022

1 Objective and Scope

The purpose of this addendum is to review updates to the Risk Evaluation and Mitigation Strategy (REMS) and Pharmacovigilance Plan (PVP) submitted under the original BLA 125746/0 for CARVYKTI® (ciltacabtagene autoleucel).

2 Updates to Risk Evaluation and Mitigation Strategy (REMS)

The sponsor made several edits to the REMS materials. Specifically, these updates included:

- Addition of CRS and ICANS grading by the 2019 ASTCT criteria, addition of organ toxicity that may occur with CRS, and CRS management to the Training Program slides (STN125746/0.61).
- Clarification of CAPA processes in the REMS Audit Protocol and edits to retraining requirements if Carvykti is not infused at least once annually from the date of initial REMS Program certification in the REMS Audit Questionnaire and REMS Audit Questionnaire Review Form (STN125746/0.61).
- Edits to the REMS Supporting Document and alignment of the REMS Assessment Plan with other CAR T products (STN125746/0.62).

Reviewer comment: The sponsor proposes to not include stratification of Carvykti utilization and compliance by healthcare facility type since this information not being collected on the Hospital Enrollment Form and collection of this information will be burdensome to healthcare sites. FDA agrees with the sponsor justification.

- Revised item 14 of the REMS Document to include that staff involved with prescribing, dispensing, or administering Carvykti should be trained using the Training Program and the Adverse Reaction Management Guide (STN125746/0.67).

Reviewer comment: DE agrees with the sponsor justification to note that staff should be trained with both the Training Program and the Adverse Reaction Management Guide as these are both items healthcare providers are required to review as part of REMS Program certification. The sponsor performed the above revision following submission of the REMS Document for OCC clearance. The revision was discussed with CDER/DRM and OCC who concurred this revision to the REMS Document was acceptable.

- Addition of management of CRS in clinical trial patients, draft information on Parkinsonism, cranial nerve palsies and management, peripheral neuropathies including Guillain-Barre Syndrome (GBS) and management, and draft information on prolonged and recurrent cytopenias to the Training Program slides (STN125746/0.67).
- Addition of Knowledge Assessment questions on peripheral neuropathies, including GBS, and prolonged or recurrent cytopenias (STN125746/0.67).

- Edits to the Training Program slides on CRS management of clinical trial subjects, Parkinsonism symptoms and grading, and management of clinical trial patients with prolonged or recurrent cytopenia (STN125746/0.69).
- Edits to the Training Program slides regarding Parkinsonism criteria and classification of the GBS patient. The sponsor requested to remove reference to the patient in another clinical trial that developed Parkinsonism. The sponsor also declined an FDA request to remove information about reduction in tumor burden as a preventative measure to prevent Parkinsonism (STN125746/0.77). Additional edits to REMS materials were made to align with the USPI.

Reviewer comment: FDA does not agree with the sponsor justification to include a slide on risk factors for developing Parkinsonism as there were only five patients in this trial and other patients with the sponsor's suggested risk factors did not develop this condition. The sponsor should also mention that a patient in another trial with ciltacabtagene autoleucel developed Parkinsonism, although it is not necessary to provide the full patient details from other clinical studies given that these studies are still ongoing.

- Edits to the Training Program slides on language and formatting of the Boxed Warnings to align with the label, addition of a slide on preparing the patient for Carvykti administration, specification of subtypes of neurologic toxicity, and addition of clinical details for peripheral neuropathy and cranial nerve palsies (STN125746/0.80). The sponsor agreed to delete the slide on Parkinsonism risk factors and add that this syndrome occurred in other clinical trials. Symptoms for cranial nerve palsy, peripheral neuropathies, and GBS were added to the Patient Wallet Card. The sponsor also added information on non-compliance with access to tocilizumab due to the shortage during the COVID-19 pandemic to the REMS Supporting Document.
- Edits to the Training Program slides to align with label and addition of “tremor” to the Patient Wallet Card (STN125746/0.81).

The sponsor also updated the REMS materials to align with the Boxed Warnings, Warnings and Precautions, and other labeling information proposed by the OTAT clinical team. The final version of the REMS Document and materials were submitted on February 28, 2022.

Reviewer comment: FDA requested that the final REMS materials be aligned with the content and language agreed to in the final label. The goals of the Carvykti REMS remain the same: to mitigate the risks of cytokine release syndrome (CRS) and neurologic toxicity (NT) by 1) ensuring hospitals and associated clinics that dispense Carvykti are specially certified and have immediate access to tocilizumab, and 2) ensuring that those who prescribe, dispense, or administer Carvykti are aware of how to manage the risks of CRS and NT. There are no changes to the REMS program elements to assure safe use (ETASU). The AEs of Parkinsonism, peripheral neuropathies including GBS, and cranial nerve palsies are considered a type of neurotoxicity and thus included within the REMS goals.

3 Updates to the Pharmacovigilance Plan (PVP)

The sponsor made the following revisions to the PVP:

- Revision of the PMR milestones following the major amendment designation (STN125746/0.71). The revised milestones are

Final protocol submission: April 30, 2022

Study Completion: June 30, 2041

Final report submission: June 30, 2042

- Addition to the PVP that spontaneous reports of GBS will be submitted to FAERS as an expedited report regardless of seriousness or relatedness, and to include a summary and analysis of GBS cases in the Periodic Adverse Experience Report (STN125746/0.75).

Reviewer comment: Two subjects, one each in CARTITUDE-2 and CARTITUDE-4, developed GBS. GBS has not previously been associated with CAR T products and thus enhanced pharmacovigilance was requested. As noted above, information on GBS has been added to the REMS Training Program slides and Knowledge Assessment.

4 DE Conclusions and Recommendations

The sponsor updated the REMS program materials to align with the package insert. The revised PVP, version 1.3 and dated January 24, 2022, is adequate for post-market safety monitoring should the product be approved. Please see the final version of the REMS Document, REMS materials, and package insert submitted by the sponsor for the final agreed-upon content and language.