



Our STN: BL 125746/0

BLA APPROVAL
February 28, 2022

Janssen Biotech, Inc.
Attention: Nancy Nair, Pharm D, MBA
920 US Highway 202
P.O. Box 300
Raritan, NJ 08869

Dear Dr. Nair:

Please refer to your Biologics License Application (BLA) submitted and received March 31, 2021, under section 351(a) of the Public Health Service Act (PHS Act) for ciltacabtagene autoleucel.

LICENSING

We have approved your BLA for ciltacabtagene autoleucel effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, ciltacabtagene autoleucel under your existing Department of Health and Human Services U.S. License No. 1864. Ciltacabtagene autoleucel is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: 03548207; 04133636; and 04181827.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture the ciltacabtagene autoleucel drug product at Janssen Pharmaceuticals, Inc. at (b) (4) [REDACTED].
The lentiviral vector will be manufactured by Janssen Vaccines (b) (4) [REDACTED].

You may label your product with the proprietary name CARVYKTI and market it in infusion bags containing a 30mL or 70mL cell suspension of $0.5-1.0 \times 10^6$ CAR-positive viable T cells per kg body weight up to a maximum of 1×10^8 viable CAR-positive T cells.

ADVISORY COMMITTEE

We did not refer your application to an Advisory Committee because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

DATING PERIOD

The dating period for ciltacabtagene autoleucel shall be 9 months from the date of manufacture when stored at $\leq -120^{\circ}\text{C}$. The date of manufacture shall be defined as the date of final formulation of the drug product. The dating period for the lentiviral vector shall be (b) (4) when stored at (b) (4). We have approved the stability protocol in your license application for the purpose of extending the expiration dating period of your lentiviral vector under 21 CFR 601.12.

COMPARABILITY PROTOCOL

Under 21 CFR 601.12(e), approval of a comparability protocol may justify a reduced reporting category for a particular change. In your annual report (21 CFR 601.12(d)), you should report information confirming that the following changes meet the requirements specified in your approved comparability protocol. Include the information described in 21 CFR 601.12(d)(3).

(b) (4)

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Under 21 CFR 601.12(e), approval of a comparability protocol may justify a reduced reporting category for a particular change. You should report information confirming that the following changes meet the requirements specified in your approved comparability protocol as a **Supplement – Changes Being Effected in 30 Days** (21 CFR 601.12(c)). You should include the information described in 21 CFR 601.12 (b)(3) in this supplement. Although you may distribute the product made using this change 30 days after FDA receives the supplement, continued distribution of the product made with the change will be subject to our final approval of the supplement.

(b) (4)

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(b) (4) [Redacted]

You should report information confirming that the following change meets the requirements specified in your approved comparability protocol as a Prior Approval Supplement (21 CFR 601.12(b)). You should include the information described in 21 CFR 601.12 (b)(3) in this supplement. Subsequent to the approval of your Prior Approval Supplement, you may distribute the product made using this change.

- (b) (4) [Redacted]

FDA LOT RELEASE

You are not currently required to submit samples or protocols of future lots of ciltacabtagene autoleucl to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2(a). We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to the Director, Office of Compliance and Biologics Quality, electronically through the eBPDR web application or at the address below. Links for the instructions on completing the electronic form (eBPDR) may be found on CBER's web site at <https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/biological-product-deviations> :

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of ciltacabtagene autoleucel, or in the manufacturing facilities.

LABELING

Under 21 CFR 201.57(c)(18), patient labeling must be referenced in section 17 PATIENT COUNSELING INFORMATION. Patient labeling must be available and may either be reprinted immediately following the full prescribing information of the package insert or accompany the prescription product labeling.

We hereby approve the draft package insert labeling submitted under amendment 83, dated February 28, 2022 and the draft carton and container labels submitted under amendment 77, dated February 4, 2022.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (SPL) format via the FDA automated drug registration and listing system, (eLIST) as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the Package Insert submitted on February 28, 2022. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND CONTAINER LABELS

Please electronically submit final printed carton and container labels identical to the carton and container labels submitted on February 4, 2022, according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at <https://www.fda.gov/downloads/drugs/guidancecompliance/regulatoryinformation/guidances/ucm333969.pdf>.

All final labeling should be submitted as Product Correspondence to this BLA, STN BL 125746/0 at the time of use and include implementation information on Form FDA 356h.

ADVERTISING AND PROMOTIONAL LABELING

You may submit two draft copies of the proposed introductory advertising and promotional labeling with Form FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and you must submit distribution reports as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format —Postmarketing Safety Reports* at <https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm458559.pdf> and FDA's Adverse Event reporting System website at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm>. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm>.

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable because sufficient numbers of pediatric patients with relapsed or refractory multiple myeloma do not exist.

Additionally, this product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients with relapsed/refractory B-cell tumors. Also, there is a lack of knowledge regarding the relevance of B-Cell Maturation Antigen (BCMA) as a potential target in pediatric relapsed/refractory B-cell tumors; therefore, this product is not likely to be used in a substantial number of pediatric patients.

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to identify a serious risk of secondary malignancies associated with the use of ciltacabtagene autoleucel. Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, we have determined that you are required to conduct the following study:

1. A post-marketing, prospective, multi-center, observational study to assess the long-term safety of ciltacabtagene autoleucel and the risk of secondary malignancies occurring after treatment with ciltacabtagene autoleucel. The study will include at least 1500 adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody; the enrolled patients will be followed for 15 years after product administration.

We acknowledge the timetable you submitted on January 5, 2022, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: April 30, 2022

Study Completion Date: June 30, 2041

Final Report Submission: June 30, 2042

Please submit the protocol to your IND 18080, with a cross-reference letter to this BLA, STN BL 125746/0 explaining that this protocol was submitted to the IND. Please refer

to the sequential number for each study/clinical trial and the submission number as shown in this letter.

Please submit final study reports to the BLA. If the information in the final study report supports a change in the label, the final study report must be submitted as a supplement to this BLA, STN BL 125746/0. For administrative purposes, all submissions related to this postmarketing study required under section 505(o) must be submitted to this BLA and be clearly designated as:

- **Required Postmarketing Correspondence under Section 505(o)**
- **Required Postmarketing Final Report under Section 505(o)**
- **Supplement contains Required Postmarketing Final Report under Section 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

You must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing requirement;
- the original milestone schedule for the requirement;
- the revised milestone schedule for the requirement, if appropriate;
- the current status of the requirement (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status for the study or clinical trial. The explanation should include how the study is progressing in reference to the original projected schedule, including the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our website at <http://www.fda.gov/Drugs/Guidance/ComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm>.

We will consider the submission of your annual report under section 506B of the FDCA and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in section 505(o) and 21

CFR 601.70. We remind you that to comply with section 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to periodically report on the status of studies or clinical trials required under section 505(o) may be a violation of FDCA section 505(o)(3)(E)(ii) and could result in regulatory action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for CARVYKTI to ensure the benefits of the drug outweigh the risks of cytokine release syndrome (CRS) and neurological toxicities.

Your proposed REMS must include the following:

Elements to assure safe use: Pursuant to section 505-1(f)(1), we have determined that CARVYKTI can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risks for CRS and neurological toxicities. Your REMS includes the following elements to mitigate these risks:

- Health care settings that dispense CARVYKTI are specially certified;
- CARVYKTI is dispensed to patients only in certain health care settings.

Implementation System: The REMS must include an implementation system to monitor and evaluate the implementation of the elements to assure safe use (outlined above) which require health care settings that dispense the drug to be specially certified and the drug be dispensed to patients only in certain health care settings, specifically, certified hospitals and their associated clinics with appropriate access to tocilizumab. The implementation system should also include an intervention plan to address any findings of non-compliance with elements to assure safe use and to address any findings that suggest an increase in risk to patients.

Your proposed REMS, submitted on February 28, 2022, and appended to this letter, is approved. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The REMS assessment plan must include, but is not limited to, the following:

For the first (6-month) CARVYKTI REMS assessment only, provide the following operational metrics:

- A. Date the CARVYKTI REMS website went live;
- B. Date the REMS call center was operational;

- C. Date REMS Certified Care Centers were able to complete the CARVYKTI REMS certification process;
- D. Date of first notification of hospital and their associated clinic certification;

For the 12-month and subsequent annual assessments:

The REMS Program Infrastructure and Performance (provide in tabular format as appropriate)

- A. Hospitals and their associated clinics enrollment and education statistics (provide for each reporting period and cumulatively)
 - List of all CARVYKTI REMS Certified Care Centers. Include locations, dates of enrollment, and method of enrollment and dates of certification notification;
 - Number of incomplete enrollments at the time of assessment data lock;
 - Number, format, and date of training on CARVYKTI REMS;
 - Number of knowledge assessments completed by healthcare providers, by healthcare provider type, including method of completion, completed by Certified Care Center personnel, other than the authorized representative, by Certified Care Center;
 - Mean and range of attempts to successfully complete the Knowledge Assessment;
 - Summary of most frequently missed Knowledge Assessment questions;
 - Number of Certified Care Centers that require retraining due to the absence of any CARVYKTI dispensing at least once annually from the date of certification in the CARVYKTI REMS.
- B. Utilization of CARVYKTI
 - Number of CARVYKTI shipments sent to Certified Care Centers (current reporting period and cumulative). Include the following demographics if available: age;
 - Number of unique patients treated with CARVYKTI at each Certified Care Center;
 - Number and age of patients for which CARVYKTI was ordered but never infused and the reason(s) that the patient was not treated; provide number of occurrences at each Certified Care Center for each reporting period and cumulatively;
 - Time between certification and first order for CARVYKTI for each Certified Care Center during the assessment period.
- C. Compliance with CARVYKTI REMS
 - Number and name of non-certified hospital(s) that have treated a patient with CARVYKTI and any corrective actions taken to prevent future

occurrences and the number of these that subsequently became certified (current reporting period and cumulative)

- Audits: A summary of findings from first-order audits and annual audits (current reporting period) by type of audit deficiencies
- Summary report of all non-compliance, associated corrective and preventative actions (CAPA), and the status of CAPA plans.

D. CARVYKTI REMS Customer Care Center

- Number of calls received by stakeholder type (patient/guardian, prescriber, hospital and their associated clinic authorized representative, other health care provider [HCP], other) and reason for the call;
- Summary of frequently asked questions (FAQ) by stakeholder type;
- A description of each call, including stakeholder type, that may indicate an issue with product access due to the REMS program, REMS program burden, or an adverse event;
- A summary of corrective or preventive actions resulting from issues identified;
- Summary of any non-compliance that is identified through call center contacts, source of report and resulting corrective and preventative actions.

E. An evaluation of understanding of the risks and mitigation strategies of the CARVYKTI REMS as well as compliance with the mitigation strategies in those who prescribe, dispense, or administer CARVYKTI, as well as hospital and their associated clinic-authorized representatives.

F. With respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified (Section 505-1(g)(3)).

Knowledge, Attitudes, and Behavior (KAB) surveys will be conducted with those who prescribe, dispense, or administer CARVYKTI, as well as hospital-authorized representatives, in order to assess their awareness and understanding of the risks of CARVYKTI and the mitigation strategies as outlined in the REMS goals and objectives.

The methodology and the knowledge, attitudes, and behavior (KAB) protocols and survey instruments should be submitted to the Agency for review at least 90 days before the surveys are initially administered.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

- a. An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b. A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c. If the new, proposed indication for use introduces unexpected risks: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d. If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.
- e. If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use: Provision of as many of the currently listed assessment plan items as is feasible.
- f. If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS.
- g. If you are not proposing a REMS modification, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**BLA 125746 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)**

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

BLA 125746 REMS ASSESSMENT

or

**NEW SUPPLEMENT FOR BLA 125746
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR BLA 125746
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR BLA 125746
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT [125746/#####]**

or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125746 REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR BLA 125746

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format. FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend

to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

POST-APPROVAL FEEDBACK MEETING

New biological products qualify for a post-approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application.

Sincerely,

Wilson W. Bryan, MD
Director
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research

Enclosures:REMS