



Our STN: BL 125646/429

**SUPPLEMENT APPROVAL**

June 11, 2021

Novartis Pharmaceuticals Corporation  
Attention: John Noh, PharmD  
One Health Plaza  
East Hanover, NJ 07936

Dear Dr. Noh:

We have approved your request submitted and received on December 11, 2020, to supplement your Biologics License Application (BLA) under section 351(a) of the Public Health Service Act for tisagenlecleucel to update the safety sections of the U.S. prescribing information (USPI), and modify the Risk Evaluation and Mitigation Strategies (REMS), based on updated data from studies CCTL019B2202 (B2202) and CCTL019C2201 (C2201).

## **LABELING**

We hereby approve the draft content of the labeling package insert submitted under amendment 26 dated June 8, 2021.

## **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 June 8, 2020. 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.

All final labeling should be submitted as Product Correspondence to this BLA, STN BL 125646/0 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)).

Please submit an amendment to all pending supplemental applications for this BLA that include revised labeling incorporating a revised content of labeling that includes this change.

## **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

The REMS for Tisagenlecleucel was originally approved on August 30, 2017. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modification to the REMS consists of revised REMS Training Slides and REMS Program website screenshots to align with the revisions to the USPI based on updated clinical trial safety data for CRS and neurologic toxicity.

Your proposed modified REMS, submitted on June 2, 2021, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on August 30, 2017.

There are no changes to the REMS assessment plan described in our August 30, 2017, letter.

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) of the FDCA. 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 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 REMS modifications,* 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 125646 REMS 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 125646 REMS ASSESSMENT**

*or*

**NEW SUPPLEMENT FOR BLA 125646  
CHANGES BEING EFFECTED IN 30 DAYS  
PROPOSED MINOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR BLA 125646  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED MAJOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR BLA 125646  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES  
SUBMITTED IN SUPPLEMENT XXX**

*or*

**NEW SUPPLEMENT (NEW INDICATION FOR USE)  
FOR BLA 125646 ]  
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 REVISIONS FOR BLA 125646**

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).

We will include information contained in the above-referenced supplement in your BLA file.

Sincerely,

Tejashri Purohit-Sheth, MD  
Director  
Division of Clinical Evaluation  
and Pharmacology/Toxicology  
Office of Tissues and Advanced Therapies  
Center for Biologics Evaluation and Research