Our STN: BL 125643/248

**SUPPLEMENT APPROVAL**
April 2, 2021

Kite Pharma, Inc.
Attention: Vip Patel
2400 Broadway
Santa Monica, CA 90404

Dear Mr. Patel:

Please refer to your supplement to your Biologics License Application (BLA) submitted September 3, 2020, received September 4, 2020, under section 351(a) of the Public Health Service Act (PHS Act) for axicabtagene ciloleucel.

We also refer to our supplement approval letter dated March 5, 2021, and provide the following update:

> Include the correct approved prescribing information label's date and amendment.

This replacement approval letter incorporates this update. The effective approval date will remain March 5, 2021, the date of the original supplement approval letter.

We have approved your request submitted September 3, 2020, received September 4, 2020, to supplement your Biologics License Application (BLA) under section 351(a) of the Public Health Service Act for axicabtagene ciloleucel to include a new indication for adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy, according to the regulations for accelerated approval [21 CFR 601.41].

The review of this supplement was associated with the following National Clinical Trial (NCT) number(s): 03105336, 02348216, 03153462, 03761056.

## ACCELERATED APPROVAL REQUIREMENTS

Under accelerated approval regulations, we may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. This approval requires you to study the biological

product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome.

Approval under these regulations requires, among other things, that you conduct an adequate and well-controlled clinical trial to verify and describe clinical benefit attributable to this product. Clinical benefit is evidenced by effects such as favorable progression-free survival demonstrated in a randomized clinical trial comparing axicabtagene ciloleucel to the standard of care.

**Accelerated Approval Required Studies**

We remind you of your postmarketing requirement specified in your submission of January 25, 2021.

1. A randomized phase 3 trial of axicabtagene ciloleucel in patients with relapsed or refractory follicular lymphoma. Patients will be randomized to axicabtagene ciloleucel or to an investigator's choice of regimens consistent with the standard of care. The primary endpoint will be progression-free survival, with secondary endpoints that include objective response rate and overall survival.

   Final Protocol Submission: August 31, 2021

   Study/Trial Completion: June 30, 2027

   Final Report Submission: September 30, 2027

We expect you to complete design, initiation, accrual, completion, and reporting of these studies within the framework described in your letter of January 25, 2021.

You must conduct this study with due diligence. If postmarketing studies fail to verify that clinical benefit is conferred by axicabtagene ciloleucel, or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43 (b), withdraw or modify approval if:

- A postmarketing clinical study fails to verify clinical benefit
- The applicant fails to perform the required postmarketing study with due diligence
- Use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the biological product
- The applicant fails to adhere to the postmarketing restrictions agreed upon
- The promotional materials are false or misleading
- Other evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use

Please submit the protocol to your IND 16278 with a cross-reference letter to BLA 125643/0 explaining that this protocol was submitted to the IND. Please refer to the sequential number for this study and the submission number as shown in this letter.

Your accelerated approval postmarketing requirement study is subject to the reporting requirements of 21 CFR 601.70, and 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 BLA until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released.

**Please submit the final study report as an efficacy supplement to BLA 125643/0.** For administrative purposes, all submissions related to this postmarketing study requirement must be clearly designated as "Subpart E Postmarketing Study Requirements."

**LABELING**

We hereby approve the draft content of labeling for your Package Insert submitted under amendment 44, dated March 12, 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. 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.

All final labeling should be submitted as Product Correspondence to this BLA 125643/0 at the time of use (prior to marketing) and include implementation information on Form FDA 356h.

**PROMOTIONAL MATERIALS**

Please note that the accelerated approval regulation concerning promotional materials (21 CFR 601.45) stipulates that all advertising and promotional labeling items that you wish to distribute in the first 120 days following approval, must have been received by FDA prior to the approval date. After approval, promotional items intended for dissemination after the first 120 days following approval must be submitted to the FDA

at least 30 days prior to the anticipated distribution date. Please submit draft materials with a cover letter noting that the items are for accelerated approval and an accompanying 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 advertisement and promotional labeling at the time of initial dissemination or publication, accompanied by FORM FDA 2253 (21 CFR 601.12(f)(4)).

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf.

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 these changes.

**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.

Because the biological product for this indication has an orphan drug designation, you are exempt from this requirement.

**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 use of axicabtagene ciloleucel in adult patients with relapsed or refractory follicular lymphoma.

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:

2. A postmarketing multicenter, prospective, observational study to assess the long-term safety of axicabtagene ciloleucel and the risk of secondary malignancies occurring after treatment with axicabtagene ciloleucel. The study will include at least 300 adult patients with relapsed or refractory follicular lymphoma; the enrolled patients will be followed for 15 years after the product administration.

   We acknowledge the time table you submitted on March 1, 2021, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: June 30, 2021

   Study Completion Date: June 30, 2041

   Final Report Submission: June 30, 2042

Please submit the protocol to your IND 16278 with a cross-reference letter to BLA 125643/0 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 labeling, the final study report must be submitted as a supplement to BLA 125643/0. 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 the approval of BLA 1257643/0 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/GuidanceComplianceRegulatoryInformation/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 (REMS) REQUIREMENTS**

The “YESCARTA and TECARTUS REMS” was originally approved on July 24, 2020 and consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The most recent REMS modification under STNs BL 125703/32 and BL 125643/259 is approved on March 5, 2021 and includes changes to the REMS training material to

align with labeling changes related to your new indication for adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy.

The timetable for submission of assessments of the REMS remains the same as that approved on July 24, 2020.

There are no changes to the REMS assessment plan described in our July 24, 2020, letter.

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