DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

March 9, 2026

Novartis Pharmaceuticals Corporation
Attention: Michelle Santiago
Associate Director Regulatory Advertising & Promotion
One Health Plaza
East Hanover, NJ 07936

RE: KYMRIAH (tisagenlecleucel)
BLA 125646/1010, 1013, 1014, 1016, 1017, 1019, 1021, 1022, 1023

Dear Ms. Santiago:

The Advertising and Promotional Labeling Branch (APLB) of the U.S. Food and Drug Administration (FDA) has reviewed various promotional materials for KYMRIAH® (tisagenlecleucel) suspension, for intravenous infusion, from Novartis Pharmaceuticals Corporation (Novartis) that include exploratory analyses, such as Progression-Free Survival (PFS) data and Overall Survival (OS) data, in conjunction with representations or suggestions that KYMRIAH is effective for these types of clinical benefits. See, for example:

- Sales Aid (FA-11463890) KYMRIAH FL 4 Year Update Leave Behind PRINT Label Update 6-25
- Sales Aid (FA-11463891) KYMRIAH FL 4 Year Update Digital Leave Behind Label Update 6-25
- Promotional Labeling (FA-11469700) KYMRIAH ALL ELIANA Flashcard Label Update 6-25
- www-website (FA-11463107) KYMRIAH FL HCP Website Label Update 6-25
- Promotional Labeling (FA-11360960) FL Reference Leave Behind Update Print 07-25
- Sales Aid (FA-11463380) KYMRIAH FL & DLBCL Digital Core Visual Aid Label Update 6-25

The promotional materials make false or misleading claims and representations about the benefits of KYMRIAH. Thus, the promotional materials misbrand KYMRIAH within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and make its distribution violative. 21 U.S.C. 321(n); 331(a); 352(a), (n). See 21 CFR 202.1(e)(5). These violations are particularly concerning from a public health perspective because the promotional materials make misleading representations about KYMRIAH being more effective or having greater clinical benefit than has been demonstrated. This may cause doctors and patients to inaccurately weigh the risks versus benefits of treatment with KYMRIAH, which can be fatal or life-threatening.

Background

According to the FDA-approved prescribing information (PI) for KYMRIAH:

> KYMRIAH is a CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of:
>
> - Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.
> - Adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.
>
> Limitations of Use: KYMRIAH is not indicated for treatment of patients with primary central nervous system lymphoma.
>
> - Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

The PI for KYMRIAH also includes a BOXED WARNING and WARNINGS AND PRECAUTIONS including, but not limited to, fatal or life-threatening reactions of Cytokine Release Syndrome, fatal or life-threatening neurological toxicities, secondary malignancies, fatal or life-threatening Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome, fatal or life-threatening serious infections, prolonged cytopenia, and hypogammaglobulinemia and agammaglobulinemia related to B-cell aplasia. The accelerated approval pathway can allow for earlier approval of drugs intended to treat serious conditions and fill an unmet medical need. Accelerated approval is based on an effect on a surrogate or intermediate clinical endpoint that is thought to be reasonably likely to predict clinical benefit, rather than on a direct measurement of clinical benefit. FDA has required sponsors of drugs approved under the accelerated approval pathway, including KYMRIAH, to conduct a confirmatory trial to verify and describe the clinical benefit of the drug.[1]

KYMRIAH studies, ELARA and ELIANA, were designed as multicenter, open-label, single-arm trials (i.e., with no comparator arm). Efficacy for the FL indication was based on objective response rate (ORR) and the duration of response (DOR); and the efficacy for the ALL indication was based on complete remission (CR) within 3 months after infusion and the duration of CR, and proportion of patients with CR and minimal residual disease (MRD), and duration of remission.

[1] We note that the confirmatory trial for KYMRIAH, a Phase 3 Trial Comparing Tisagenlecleucel to Standard of Care in Adult Participants with r/r Follicular Lymphoma is currently ongoing and has not been completed (See: https://clinicaltrials.gov/study/NCT05888493?term=tisagenlecleucel&aggFilters=status:com%20act%20rec&page=2&rank=15)

False or Misleading Benefit Presentation

Prescription drug advertisements and labeling (promotional communications) misbrand a drug if they are false or misleading with respect to efficacy. The determination of whether a promotional communication is misleading includes, among other things, not only representations made or suggested in the promotional communication, but also the extent to which the promotional communication fails to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the promotional communication. See section 201(n) of the FD&C Act, 21 U.S.C. 321(n).

You include representations in KYMRIAH's promotional materials suggesting that it is effective in providing PFS and OS benefits. For example, KYMRIAH's promotional materials include headlines such as: "**An estimated 50% of patients treated with KYMRIAH were progression free at 48 months**," and "**An estimated 79% of patients treated with KYMRIAH were still alive 48 months after infusion**." Additionally, the Flash Card includes 5-year OS and relapse-free survival (RFS) graphs at 60.1 months from the ELIANA trial, and the healthcare provider website and the Reference Leave Behind include graphs and representations regarding OS and PFS from the ELARA trial.

Your presentations include data for time-to-event endpoints from single-arm trials, such as PFS and OS, that have statistical limitations rendering such endpoints uninterpretable. The efficacy of KYMRIAH for the FL indication was established from the ELARA study, on the basis of ORR and DOR. The efficacy for the ALL indication was established from the ELIANA study, based on CR, MRD, and duration of remission. In the absence of an appropriate comparator for KYMRIAH, it is not possible to determine if the observed effect you represented is attributable to KYMRIAH or to other factor(s), such as the natural history of the disease. Consequently, your promotional advertising and labeling that represents or suggests KYMRIAH is effective in providing PFS or OS is misleading.

We acknowledge that your presentations include, but are not limited to, the following statements (in smaller less prominent font) appearing with the PFS and OS presentations:

- *PFS data should be interpreted with caution in a single-arm trial as the statistical significance is unknown*
- *Time to next anti-lymphoma treatment was an exploratory end point in the ELARA trial and should be interpreted with caution*
- *OS data should be interpreted with caution in a single-arm trial as the statistical significance is unknown*

However, these statements and references do not sufficiently mitigate the overall misleading message conveyed by these materials.

Conclusion and Requested Action

For the reasons discussed above, your promotional materials misbrand KYMRIAH within the meaning of the Act and make its distribution violative. See 21 U.S.C. 321(n), 331(a), and 352(a), (n); 21 CFR 202.1(e)(5).

This letter notifies you of our concerns and provides you with an opportunity to address them. APLB requests that you cease any violations of the FD&C Act. Within 15 working days of receipt, please submit a written response to this letter addressing the concerns described, listing all advertising and promotional labeling materials (including the dissemination/publication date and Material ID Code) for KYMRIAH that contain the same or similar representations or suggestions, and explaining your plans for discontinuation of such.

If you believe that your product is not in violation of the FD&C Act, please include in your submission to us your reasoning and any supporting information for our consideration within 15 working days from the date of receipt of this letter.

The concerns discussed in this letter do not constitute an exhaustive list of potential violations. It is your responsibility to ensure compliance with all applicable requirements of the FD&C Act and its implementing regulations.

Please submit your response to your eCTD under the heading 1.15.1.6 and email a copy of your response to CBERAPLB@fda.hhs.gov. We remind you that only written communications are considered official responses. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter and refer to the BLA/STN numbers.

Questions related to the submission of your response letter should be emailed to CBERAPLB@fda.hhs.gov.

Sincerely,

Melissa Mendoza, J.D.
Office Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research