NDA 218730/S-003

SUPPLEMENT APPROVAL

Vertex Pharmaceuticals Incorporated
Attention: Thiago Loureiro
Associate Director, Regulatory Affairs
50 Northern Avenue
Boston, MA 02210

Dear Dr. Thiago Loureiro:

Please refer to your supplemental new drug applications (sNDA) dated and received February 18, 2026, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Alyftrek (vanzacaftor/ tezacaftor/ deutivacaftor) tablets.

We also refer to our letter dated December 4, 2025, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we have determined should be included in the labeling for Alyftrek. This information pertains to the risk of psychiatric disorders.

This supplemental new drug application provides for revisions to the labeling for Alyftrek. The agreed upon changes to the language included in our December 4, 2025, letter are as follows (additions are noted by underline and deletion are noted by ~~strikethrough)~~.

HIGHLIGHTS OF PRESCRIBING INFORMATION

RECENT MAJOR CHANGES

Warnings and Precautions, Neuropsychiatric Events, Including ~~Suicidality~~ Suicidal Thoughts and Behaviors (5.5) MM/YYYY

WARNINGS AND PRECAUTIONS

- Neuropsychiatric Events, including ~~Suicidality~~ Suicidal Thoughts and Behaviors: Serious neuropsychiatric events, including symptoms of anxiety, depression, suicidal ideation and behavior, and sleep disturbances, have been reported in the postmarketing setting for ALYFTREK or drugs containing the same or similar active ingredients. Monitor patients closely for new or worsening symptoms. Consider the risks and benefits for the individual patient to determine if therapy with

ALYFTREK should be interrupted at the occurrence of neuropsychiatric symptoms. (5.5)

FULL PRESCRIBING INFORMATION: CONTENTS*

5 WARNINGS AND PRECAUTIONS

5.5 Neuropsychiatric Events, Including ~~Suicidality~~ Suicidal Thoughts and Behaviors

Serious neuropsychiatric events, including symptoms of anxiety, depression, suicidal ideation and behavior, and sleep disturbances, have been reported in the postmarketing setting in patients taking ALYFTREK or drugs containing the same or similar active ingredients. The events were reported in adult and pediatric patients with and without a previous history of neuropsychiatric symptoms. Symptoms ~~can~~ may occur ~~as early as the~~ within the first three months of ~~therapy~~ treatment initiation.

Assess patients for baseline neuropsychiatric symptoms and monitor for new or worsening symptoms of anxiety, depression, suicidal ideation or behavior, or sleep disturbances. Consider the benefits and risks for the individual patient to determine if therapy with ALYFTREK should be interrupted at the occurrence of neuropsychiatric symptoms and whether to resume therapy with symptom improvement.

6 ADVERSE REACTIONS

- Neuropsychiatric Events, Including ~~Suicidality~~ Suicidal Thoughts and Behaviors *[see Warnings and Precautions (5.5)]*

17 PATIENT COUNSELING INFORMATION

Neuropsychiatric Events, Including ~~Suicidality~~ Suicidal Thoughts and Behaviors

Inform patients that neuropsychiatric symptoms, including anxiety, depression, suicidal thoughts and behaviors, and sleep disturbances (e.g., insomnia), have been reported with the use of ALYFTREK or drugs containing the same or similar active ingredients as ALYFTREK. The symptoms have been observed in patients with and without a history of similar symptoms and ~~have occurred as early as the first~~ may occur within three months of ALYFTREK initiation. Instruct patients to contact their healthcare provider immediately if changes in behavior or thinking that are

not typical for the patient occur, or if the patient develops suicidal ideation or behavior *[see Warnings and Precautions (5.5)]*.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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.

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[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Because none of these criteria apply to your supplemental application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety- related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, contact Elaine Sit, Regulatory Project Manager, at (301) 796-5073 or elaine.sit@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Banu Karimi-Shah, MD
Director
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BANU A KARIMI SHAH
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