NDA 212273/S-012
NDA 217660/S-003

CORRECTED SUPPLEMENT APPROVAL

Vertex Pharmaceuticals Incorporated
Attention: Ryan McGlynn, PhD
Manager, Regulatory Affairs
50 Northern Ave
Boston, MA 02210

Dear Dr. McGlynn:

Please refer to your supplemental new drug applications (sNDAs) dated and received, February 22, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Trikafta (elexacaftor/tezacaftor/ivacaftor) tablets and granules.

We also refer to our approval letter dated December 20, 2024, which contained the following error(s): missing carton and container labeling for the granules.

This corrected action letter incorporates the correction of the error. The effective action date will remain December 20, 2024, the date of the original letter.

We acknowledge receipt of your major amendments dated June 20, and July 19, 2024, which extended the goal date by three months.

These Prior Approval supplemental new drug applications provide for the inclusion of additional mutations to the indication: treatment of cystic fibrosis in patients aged 2 years and older who have at least one F508del mutation in the CFTR gene or a mutation in the CFTR gene that is responsive based on clinical and/or in vitro data.

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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

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 and 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.

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

[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.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 212273/S-012, NDA 217660/S-003**." Approval of this submission by FDA is not required before the labeling is used.

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

[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

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).

REQUESTED ENHANCED PHARMACOVIGILANCE (EPV)

We request that for Trikafta you submit all serious and non-serious domestic and foreign cases of hepatic injury, received as spontaneous reports, as 15-day "Alert reports" (described under 21 CFR 314.80(c)(1) through the fifth year following the date of this letter.

We also request that you provide separate narrative summary and analysis of hepatic injury with your periodic safety report for NDA 212273. In our letter dated December 23, 2022, we granted a waiver for NDA 212273 allowing the submission of the Periodic Benefit-Risk Evaluation Report (PBRER) instead of the periodic adverse drug experience report (PADER) required under our regulations. The PBRER is to be submitted semi-annually to NDA 212273. The separate summary and analysis should include cases of hepatic injury associated with the use of Trikafta under both U.S. approved applications (NDAs 212273 and 217660). Your analysis should include interval and cumulative data relative to the date of this letter and be separated by different dosage forms, formulations, and indications. The separate summary and

analysis should be submitted with the PBRER through the fifth year following the date of this letter.

Furthermore, provide a line listing that includes the following information for each case:

- CF genotype
- TRIKAFTA dosage
- duration of therapy
- temporal association
- dechallenge/rechallenge
- associated signs and symptoms
- hepatic enzymes and liver function tests
- concomitant medications [list all, including prescription and over-the-counter medications (indication, dosage), herbal, and illicit substances]
- medical history
- hospitalizations, testing (including imaging), and treatment given for the event
- outcome at the time of the report
- assessment of causality

To identify reports of hepatic injury, we request that you use the Standardised MedDRA Querys (SMQs) Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (Broad) and Hepatitis, non-infectious (Broad).

If you have any questions, contact Cindy Chee, Regulatory Project Manager, at 301-796-0889 or cindy.chee@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

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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