NDA 212273/S-002

SUPPLEMENT APPROVAL

Vertex Pharmaceuticals
50 Northern Avenue
Boston, MA 02210

Attention: Stacy Lindmark
Manager, Global Regulatory Affairs

Dear Ms. Lindmark:

Please refer to your supplemental new drug application (sNDA) dated June 30, 2020 received June 30, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Trikafta (elexacaftor/tezacaftor/ivacaftor) tablets.

This Prior Approval supplemental new drug application proposes to expand the indication to include treatment of patients with cystic fibrosis who have a mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is responsive to elexacaftor/tezacaftor/ivacaftor based upon *in vitro* data. The revised indication is the treatment of cystic fibrosis in patients aged 12 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene or a mutation in the *CFTR* gene that is responsive based on *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.

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, Patient Package Insert), 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.

[1] 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*.[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 application, you are exempt from this requirement.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3987-1 Conduct a 3-year, single arm, observational study to further understand the clinical response to elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) and tezacaftor/ivacaftor (TEZ/IVA) in cystic fibrosis (CF) patients. The study will include all patients registered in the U.S. Cystic Fibrosis Foundation Patient Registry who do not have an F508del allele but do have a CFTR mutation that has been characterized in vitro as responsive to ELX/TEZ/IVA and/or TEZ/IVA, but not to IVA alone, and who initiate ELX/TEZ/IVA and/or TEZ/IVA therapy following the date of approval of this supplement. Patients will be followed for at least 3 years on ELX/TEZ/IVA and/or TEZ/IVA after ELX/TEZ/IVA and/or TEZ/IVA initiation. The key outcomes of interest will include lung function measurements (FEV1),

[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.

nutritional parameters (e.g., BMI), pulmonary exacerbations, hospitalizations, select CF complications (e.g., symptomatic sinus disease, CFRD, distal intestinal obstruction), and the presence of select pulmonary microorganisms (e.g., P aeruginosa).

The timetable you submitted on December 7, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2021
Final Protocol Submission:	08/2021
Interim Report:	12/2023
Study/Trial Completion:	12/2024
Final Report Submission:	12/2025

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

REPORTING REQUIREMENTS

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

If you have any questions, call Angela Ramsey, Senior Program Management Officer, at 301-796-2284.

Sincerely,

{See appended electronic signature page}

Sally Seymour, MD
Director

[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

Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

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/

SALLY M SEYMOUR
12/21/2020 08:13:38 AM