CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

218730Orig1s000

Trade Name:	Alyftrek tablets
Generic or Proper Name:	vanzacaftor/tezacaftor/deutivacaftor
Sponsor:	Vertex Pharmaceuticals Incorporated
Approval Date:	December 20, 2024
Indication:	For treatment of cystic fibrosis (CF) in patients 6 years of age and older who have at least one *F508del* mutation or another responsive mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR)* gene.

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218730Orig1s000

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

NDA 218730

NDA APPROVAL

Vertex Pharmaceuticals Incorporated
Attention: Hannah K. O'Connor
Senior Manager, Regulatory Affairs
50 Northern Ave
Boston, MA 02210

Dear Hannah O'Connor:

Please refer to your new drug application (NDA) dated May 2, 2024, received May 2, 2024, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Alyftrek (vanzacaftor/tezacaftor/deutivacaftor) tablets.

This NDA provides for the use of Alyftrek (vanzacaftor/tezacaftor/deutivacaftor) tablets for treatment of cystic fibrosis (CF) in patients 6 years of age and older who have at least one *F508del* mutation or another responsive mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR)* gene.

APPROVAL & LABELING

We have completed our review of this application. 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

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

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 *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 218730**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Alyftrek (vanzacaftor/tezacaftor/deutivacaftor) tablet shall be 24 months from the date of manufacture when stored at controlled room temperature.

ADVISORY COMMITTEE

Your application for Alyftrek (vanzacaftor/tezacaftor/deutivacaftor) tablet was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

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

[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.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) 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.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of tumorigenicity of vanzacaftor.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4734-1 Conduct a 2 year carcinogenicity study in rats administered vanzacaftor.

The timetable you submitted on December 2, 2024, states that you will conduct this study according to the following schedule:

Study Completion:	02/2025
Final Report Submission:	04/2025

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of potential increase of systemic exposure of drugs which are sensitive substrates of breast cancer resistance protein (BCRP) due to the observed in vitro inhibitory profiles of vanzacaftor and deutivacaftor on BCRP.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

4734-2 Conduct a drug-drug interaction (DDI) clinical trial to assess the effect of vanzacaftor/tezacaftor/deutivacaftor on the pharmacokinetics of a sensitive breast cancer resistance protein (BCRP) substrate.

The timetable you submitted on December 17, 2024 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	06/2025
Trial Completion:	05/2026
Final Report Submission:	11/2026

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocol(s) to your IND 142001 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o) , REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o), REQUIRED POSTMARKETING CORRESPONDENCE UNDER 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. Section 506B(a)(1) of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 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 submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

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*.[4]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication,

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

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 ALYFTREK you submit all serious and non-serious domestic and foreign cases of hepatic injury as 15-day "Alert reports" (described under 21 CFR 314.80(c)(1)) through the seventh year following the date of this letter.

As described in 21 CFR 314.80(c)(1)(ii), we request that you investigate all 15-day Alert reports of hepatic injury to obtain the data elements included in the bulleted list below.

We also request that you provide separate narrative summary and analysis of hepatic injury as part of your required periodic safety reports [e.g., periodic adverse drug experience report (PADER) required under 21 CFR 314.80(c)(2)], quarterly during the first 3 years post-approval and annually thereafter, through the seventh year following the initial U.S. approval date. The separate summary and analysis should include cases of hepatic injury associated with the use of ALYFTREK under this application (NDA 218730). The separate summary and analysis should be submitted with the PADER through the seventh year following the date of this letter.

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

- CF genotype
- ALYFTREK 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

[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

- assessment of causality

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

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[7].

If you have any questions, contact Julianne Lee, Regulatory Project Manager, at 240-402-5130 or julianne.lee@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Nikolay Nikolov, MD
Office Director
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

[7] https://www.uspnf.com/

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/

NIKOLAY P NIKOLOV
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