

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

212273Orig1s000

Trade Name: Trikafta

Generic or Proper Name: elexacaftor/ tezacaftor/ivacaftor tablets
100 mg/50 mg/75 mg and 150 mg of ivacaftor

Sponsor: Vertex Pharmaceuticals Inc.

Approval Date: October 18, 2019

Indication: For the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene.

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CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
REMS	
Officer/Employee List	X
Multidiscipline Review(s) • Summary Review • Office Director • Cross Discipline Team Leader • Clinical • Non-Clinical • Statistical • Clinical Pharmacology	X
Product Quality Review(s)	X
Clinical Microbiology / Virology Review(s)	
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	X
Proprietary Name Review(s)	X
Administrative/Correspondence Document(s)	X

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 212273

NDA APPROVAL

Vertex Pharmaceuticals
50 Northern Avenue
Boston, MA 02210

Attention: Stacey Lindmark
Senior Manager, Regulatory Affairs

Dear Ms. Lindmark:

Please refer to your new drug application (NDA) dated July 19, 2019, received July 19, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Trikafta (elexacaftor, tezacaftor and ivacaftor tablets; ivacaftor tablets).

This new drug application provides for the use of Trikafta (elexacaftor, tezacaftor and ivacaftor tablets; ivacaftor tablets) for treatment of cystic fibrosis in patients 12 years and older who have at least one F508del mutation in the CFTR gene.

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) 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 via publicly available labeling repositories.

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.” Approval of this submission by FDA is not required before the labeling is used.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV NDA 212273. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application and must include the date the sponsor intends to submit the application. This notification should be prominently marked, “Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher.”
- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.

- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.
- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:
 - o the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
 - o the estimated demand in the U.S. for the product, and
 - o the actual amount of product distributed in the U.S.
- You may also review the requirements related to this program by visiting FDA's Rare Pediatric Disease Priority Review Voucher Program web page.³

ADVISORY COMMITTEE

Your application for Trikafta was not referred to an FDA advisory committee because the clinical trial design is acceptable, and the application did not raise significant safety or efficacy issues in the intended population.

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.

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.

³ <https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/RarePediatricDiseasePriorityVoucherProgram/default.htm>

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 assess a potential serious risk of tumorigenicity of elexacaftor and a key metabolite.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

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

3718-1 Carcinogenicity study in rats

The timetable you submitted on October 1, 2019, states that you will conduct this study according to the following schedule:

Study Completion: 07/2020

Final Report Submission: 08/2021

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of increased drug toxicity due to increased systemic exposure of elexacaftor in patients with hepatic impairment.

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

3718-2 Conduct a clinical trial to evaluate the pharmacokinetics, safety and tolerability of elexacaftor in patients with hepatic impairment compared to healthy subjects

The timetable you submitted on October 1, 2019 states that you will conduct this trial according to the following schedule:

Trial Completion: 05/2020

Final Report Submission: 02/2021

Submit clinical protocol(s) to your IND 132547 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).

**POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS
UNDER SECTION 506B**

We remind you of your postmarketing commitments:

- 3718-3 Conduct an 8-week randomized, double-blind, active-controlled, parallel-arm clinical trial to evaluate the efficacy of Trikafta (elexacaftor/tezacaftor/ivacaftor) therapy in patients with cystic fibrosis 12 years of age and older who are heterozygous for the F508del mutation and a second gating or residual function mutation. For eligible genotypes, the active comparator will be a CFTR modulator chosen according to US Standard of Care (i.e., ivacaftor or tezacaftor/ivacaftor). The key outcomes of interest will include lung function measurements (percent predicted forced expiratory volume in 1 second), sweat chloride, disease specific quality of life measures (Cystic fibrosis Questionnaire-Revised Respiratory Domain), and nutritional status (i.e., body mass index).

The timetable you submitted on October 1, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 12/2019
Trial Completion: 10/2020
Final Report Submission: 06/2021

- 3718-4 Conduct a 96-week, open-label, extension study to evaluate the long-term safety of Trikafta (elexacaftor/tezacaftor/ivacaftor) in CF patients who are heterozygous or homozygous for the F508del CFTR mutation.

The timetable you submitted on October 1, 2019, states that you will conduct this study according to the following schedule:

Trial Completion: 04/2021
Final Report Submission: 02/2022

**POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING
REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments:

- 3718-5 Implementation of three tier particle size specification (D10, D50, and D90) for VX-445 particle size distribution. Submission of the

D10, D50 and D90 particle size distribution for at least five commercial batches along with complete dissolution profiles. These data along with similarity testing should be used to verify the design space for D50, revise D90 ranges and implement the ranges for D10.

Final Report Submission: 06/2020

3718-6 Implementation of three tier particle size specification (i.e., D10, D50, and D90) for (b) (4). Submission of the D10, D50 and D90 size distribution for at least five commercial batches along with complete dissolution profiles. These data along with similarity testing should be used to verify the design space and set the appropriate ranges for D10, D50 and D90.

Final Report Submission: 06/2020

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft 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,

⁴ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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 For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.⁷

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.⁸

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biological products 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.

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁶ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

⁷ <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>

⁸ <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>

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

Sincerely,

{See appended electronic signature page}

Mary Thanh Hai, MD
Acting Office Director
Office of Drug Evaluation II
Center for Drug Evaluation and
Research

ENCLOSURE(S):

- Content of Labeling
 - o Prescribing Information
 - o Patient Information
- 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/

MARY T THANH HAI
10/21/2019 01:20:22 PM