CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217660Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 19, 2023
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 217660
Product Name, Dosage Form, and Strength:	Trikafta (elexacaftor tezacaftor ivacaftor and ivacaftor) oral granules, 80 mg/40 mg/60 mg and 59.5 mg of ivacaftor 100 mg/50 mg/75 mg and 75 mg of ivacaftor
Applicant/Sponsor Name:	Vertex Pharmaceuticals Incorporated
TTT ID #:	2022-2696-2
DMEPA 2 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 2 Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on April 18, 2023 for Trikafta. Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised container labels and carton labeling for Trikafta (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Owens, L. Label and Labeling Review for Trikafta (NDA 217660). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 APR 13. TTT ID No.: 2022-2696-1.

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/s/

LISSA C PRINGLE-OWENS
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 13, 2023
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 217660
Product Name, Dosage Form, and Strength:	Trikafta (elexacaftor tezacaftor ivacaftor and ivacaftor) oral granules, 80 mg/40 mg/60 mg and 59.5 mg of ivacaftor 100 mg/50 mg/75 mg and 75 mg of ivacaftor
Applicant/Sponsor Name:	Vertex Pharmaceuticals Incorporated
TTT ID #:	2022-2696-1
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on March 31, 2023 and on April 5, 2023, for Trikafta. Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised container labels and carton labeling for Trikafta (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant provided a "partial response" to provide feedback to our recommendation: "Under the strength color block on the sachet, add the term 'morning' or 'evening' to correspond with the appropriate strength." Vertex has proposed to update the existing text on the initial supply to include the following instructions on the inside panel: "Do not remove packet until ready to take the dose – use all 7 days doses before starting a new wallet." Further, they proposed to add the recommended 'morning' and 'evening' to the corresponding sachets

[a] Owens, L. Label and Labeling Review for Trikafta (NDA 217660). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 MAR 24. TTT ID No.: 2022-2696.

after the Agency has confirmed the final text and new packaging in approximately twelve weeks.

On April 5, 2023, we sent an Information Request (IR)[b] to Vertex acknowledging the March 31, 2023, response above and stating our concerns with the security of the container closure system and potential medication errors if packets were to dislodge from the wallets. On April 7, 2023, Vertex responded[c] to the IR and stated that the samples the Agency received were not "commercially prepared packaging material." They further stated that the "TRIKAFTA granules package components will utilize the same primary and secondary packaging materials and production process as the currently available KALYDECO (first launched in 2015) and ORKAMBI (first launched in 2018) granules… and Vertex has not experienced issues or received any product quality complaints related to the packets dislodging from the wallet and falling out for any of the marketed strengths." Based on their response, we searched FAERS using the criteria in the table 1 (see Appendix B) for Kalydeco and Orkambi on April 12, 2023.[d] We did not identify any cases indicating the packaging design of the drug packets contributing to the medication error.

Additionally, we reached out to the Division (see Appendix C) regarding our concerns and "the clinical safety concerns for intermittent errors are pretty low-the medication is generally well tolerated…" Vertex has stated that they will add the recommended 'morning' and 'evening' to the corresponding sachets and via email (see Appendix C) we inquired about the quantity of the initial supply that will be released without the "morning" and "evening". They responded "Vertex has produced approximately (b) (4) low dose kits and (b) (4) high dose kits. This represents approximately 6 months of stock. This is the minimum quantity required to ensure stock is available to support launch and protect continuity of supply while the new product (including the revised artwork) is manufactured and released for distribution." The proposed label and labeling were submitted on April 5, 2023 (see Appendix D). We note that this submission addressed our previous labeling recommendations as the March 31, 2023, response was a "partial response." Based on the totality of the information provided, the proposal is acceptable, however we do have additional recommendations on the revised carton labeling to help increase the readability of the product strength presentation.

3 RECOMMENDATIONS FOR VERTEX PHARMACEUTICALS INCORPORATED

We recommend the following be implemented prior to approval of this NDA:

A. As currently presented the proposed product's 2-separate drug product's strength presentations are linked by the bolded statement "co-packaged with" and are buried within a text heavy block that is burdensome to read. Relocate the strength statement to its own independent section separate from the dosage form and remove the bold font from the dosage form statement. Additionally, remove the bold font from the statement "co-packaged with". This will allow for greater prominence to the product

[b] file:///C:/Users/OWENSL/Downloads/NDA%20217660%20Information%20Request%204-5-23.pdf
[c] \\CDSESUB1\EVSPROD\nda217660\0023\m1\us\multi-module-info-amend-resp-rcvd-05apr2023.pdf
[d] Search conducted by DMAMES Postmarket Medication Error Team (PMET)

strength presentations. Ensure that the proprietary name and established names remain as the most prominent items on the primary display panel. For example:

Trikafta
(elexacaftor tezacaftor ivacaftor and ivacaftor)
oral granules
80 mg/40 mg/60 mg and 59.5 mg
Co-packaged with
(ivacaftor) oral granules
75 mg

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Appendix B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

On April 13, 2023, we[e] searched FAERS using the criteria in the table below and identified 76 cases. We individually reviewed the cases and limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[f] We filtered cases based on "granules" We excluded 60 cases because they did not include granules. The remaining 16 cases did not indicate the packaging design of the drug packets contributed to the medication error.

Criteria Used to Search FAERS	
Initial FDA Receive Dates:	March 17, 2015 (approval date of Kalydeco granule) - April 12, 2023
Product Active Ingredient (PAI):	IVACAFTOR, IVACAFTOR\LUMACAFTOR
Drug role	Suspect
Event:	SMQ: *Medication errors* (Narrow)
Country (Derived):	USA

B.2 Results

Our search identified 16 cases, of which 0 described errors relevant for this review.

B.3 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

[e] Search conducted by DMAMES Postmarket Medication Error Team (PMET)
[f] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

Appendix C: Email Correspondence

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	March 27, 2023
To:	Katherine Won, Regulatory Project Manager **Division of Pulmonology, Allergy, and Critical Care (DPACC)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Quynh-Nhu Capasso, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name)/Dosage Form and Route:	TRIKAFTA (elexacaftor, tezacaftor, and ivacaftor tablets; ivacaftor tablets), co-packaged for oral use TRIKAFTA (elexacaftor, tezacaftor, and ivacaftor oral granules; ivacaftor oral granules), co-packaged
Application Type/Number:	NDA 217660
Applicant:	Vertex Pharmaceuticals, Inc.

1 INTRODUCTION

On October 28, 2022, Vertex Pharmaceuticals, Inc., submitted for the Agency's review an original New Drug Application (NDA) #217660 for TRIKAFTA (elexacaftor, tezacaftor, and ivacaftor tablets; ivacaftor tablets), co-packaged for oral use and TRIKAFTA (elexacaftor, tezacaftor, and ivacaftor oral granules; ivacaftor oral granules), co-packaged. The proposed indication is for the treatment of cystic fibrosis (CF) in patients aged 2 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.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonology, Allergy, and Critical Care (DPACC) on November 3, 2022, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TRIKAFTA (elexacaftor, tezacaftor, and ivacaftor tablets; ivacaftor tablets), co-packaged for oral use and TRIKAFTA (elexacaftor, tezacaftor, and ivacaftor oral granules; ivacaftor oral granules), co-packaged.

2 MATERIAL REVIEWED

- Draft TRIKAFTA (elexacaftor, tezacaftor, and ivacaftor tablets; ivacaftor tablets) and TRIKAFTA (elexacaftor, tezacaftor, and ivacaftor oral granules; ivacaftor oral granules) PPI received on October 28, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 21, 2023.
- Draft TRIKAFTA (elexacaftor, tezacaftor, and ivacaftor tablets; ivacaftor tablets) and TRIKAFTA (elexacaftor, tezacaftor, and ivacaftor oral granules; ivacaftor oral granules) Prescribing Information (PI) received on October 28, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 21, 2023.
- Approved TRIKAFTA (elexacaftor, tezacaftor, and ivacaftor tablets; ivacaftor) tablets), co-packaged for oral use labeling dated October 4, 2021.
- Approved KALYDECO comparator labeling dated December 21, 2020.
- Approved SYMDEKO comparator labeling dated December 21, 2020.
- Approved ORKAMBI comparator labeling dated September 2, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication*

Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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DMPP-OPDP review of TRIKAFTA NDA 217660 PPI

QUYNH-NHU D CAPASSO
03/27/2023 05:15:44 PM

MARCIA B WILLIAMS
03/28/2023 06:49:26 AM

LASHAWN M GRIFFITHS
03/28/2023 07:40:15 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 24, 2023

To: Katherine Won, Senior Regulatory Health Project Manager
Division of Pulmonology, Allergy, and Critical Care (DPACC)

From: Quynh-Nhu Capasso, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Team Leader, OPDP
Kyle Snyder, Regulatory Review Officer, OPDP

Subject: OPDP Labeling Comments for TRIKAFTA® (elexacaftor, tezacaftor, and ivacaftor; ivacaftor oral granules), co-packaged

NDA: 217660

Background:
In response to DPACC's consult request dated November 1, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original NDA submission for TRIKAFTA® (elexacaftor, tezacaftor, and ivacaftor; ivacaftor oral granules), co-packaged.

PI/PPI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on March 21, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed PPI, and comments will be sent under separate cover.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on March 21, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Quynh-Nhu Capasso at quynh-nhu.capasso@fda.hhs.gov.

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/s/

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 24, 2023
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 217660
Product Name, Dosage Form, and Strength:	Trikafta (elexacaftor tezacaftor ivacaftor and ivacaftor) oral granules, 80 mg/40 mg/60 mg and 59.5 mg of ivacaftor 100 mg/50 mg/75 mg and 75 mg of ivacaftor
Product Type:	Multiple Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Vertex Pharmaceuticals Incorporated
FDA Received Date:	October 28, 2022, February 7, 2023, March 8, 2023
TTT ID #:	2022-2696
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

As part of the approval process for Trikafta (elexacaftor tezacaftor ivacaftor and ivacaftor) oral granules, the Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the proposed Trikafta prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
ISMP Newsletters*	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed container labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for Vertex Pharmaceuticals Incorporated.

4 RECOMMENDATIONS FOR VERTEX PHARMACEUTICALS INCORPORATED

Table 2. Identified Issues and Recommendations for Vertex Pharmaceuticals Incorporated (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The format for expiration date is not defined.	Clearly define the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
Container Label(s)-Sachet			
1.	The sachets may not be stored in the wallet or may disengage from the wallet.	If the sachets are not stored in the wallet or disengages from the wallet, there is potential confusion with which sachet should be taken in morning/evening. This may lead to wrong dose errors.	Under the strength color block on the sachet, add the term 'morning' or 'evening' to correspond with the appropriate strength.

Table 2. Identified Issues and Recommendations for Vertex Pharmaceuticals Incorporated (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Carton Labeling			
1.	The “and” in the color blocking area is off to the side.	The “and” off to the side in the color blocking area may present confusion as to which strengths corresponds to which sachet.	Consider revising the strength presentation in the color blocking area to include “and” in the same pattern display. e.g.: 100 mg 50 mg 75 mg and 75 mg

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Error! Reference source not found. presents relevant product information for Trikafta that Vertex Pharmaceuticals Incorporated submitted on October 28, 2022.

Table 4. Relevant Product Information for Trikafta and Trikafta 212273

NDA	**217660**	**212273**
Initial Approval Date	**N/A**	**October 21, 2019**
Product Name	**Trikafta** tri-KAF-tuh	**Trikafta** tri-KAF-tuh
Initial Approval Date	N/A	October 21, 2019
Active Ingredient	elexacaftor, tezacaftor, and ivacaftor oral granules; ivacaftor oral granules	elexacaftor, tezacaftor, and ivacaftor tablets; ivacaftor tablets
Indication	the treatment of cystic fibrosis (CF) 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 in vitro data	
Route of Administration	Oral	
Dosage Form	*Oral granules*	*Oral tablets*
Strength	*100 mg/50 mg/75 mg and 75 mg of ivacaftor* *80 mg/40 mg/60 mg and 59.5 mg of ivacaftor*	*50 mg/25 mg/37.5 mg and 75 mg of ivacaftor* *100 mg/50 mg/75 mg and 150 mg of ivacaftor*
Dose and Frequency	Ages 2 to less than 6 years old: **Weight** / **Morning Dose** / **Evening Dose** Less than 14 kg: One packet containing elexacaftor 80 mg/tezacaftor 40 mg/ivacaftor 60 mg oral granules / One packet containing ivacaftor 59.5 mg oral granules 14 kg or more: One packet containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg oral granules / One packet containing ivacaftor 75 mg oral granules	Ages 6 to 12 years old: **Weight** / **Morning Dose** / **Evening Dose** Less than 30 kg: Two tablets, each containing elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg / One tablet of ivacaftor 75 mg 30 kg or more: Two tablets, each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg / One tablet of ivacaftor 150 mg 12 years and older: **Morning Dose** / **Evening Dose** Two tablets, each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg / One tablet of ivacaftor 150 mg
How Supplied	Oral granules are supplied in morning and evening unit-dose packets containing a fixed dose. The packets are placed into a printed wallet. Four wallets are placed in a printed outer carton.	Tablets are supplied in a co-packaged blister pack sealed into a printed wallet containing a fixed-dose. Four such wallets are placed in a printed outer caron.
Storage	Store at 68ºF - 77ºF (20ºC - 25ºC); excursions permitted to 59ºF - 86ºF (15ºC - 30ºC)	

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Trikafta labels and labeling submitted by Vertex Pharmaceuticals Incorporated.

- Container label(s) received on October 28, 2022
- Carton labeling received on October 28, 2022
- Prescribing Information (Image not shown) received on October 28, 2022, available from \\CDSESUB1\EVSPROD\nda217660\0001\m1\us\annotated-draft-labeling-text.pdf

F.2 Label and Labeling Images

Container label(s)

Sachets

(b) (4)

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 217660

Application Type: New NDA

Drug Name(s)/Dosage Form(s): TRIKAFTA (elexacaftor / tezacaftor / ivacaftor) and Ivacaftor Oral Granules

Applicant: Vertex Pharmaceuticals Incorporated

Receipt Date: October 28, 2022

Goal Date: April 28, 2022

1. Regulatory History and Applicant's Main Proposals

The Applicant, Vertex Pharmaceuticals Incorporated, submitted a New Drug Application (NDA) on October 28, 2022, for TRIKAFTA (elexacaftor / tezacaftor / ivacaftor) and Ivacaftor Oral Granules. The proposed indication is treatment of cystic fibrosis (CF) in patients aged 2 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. NDA 212273 TRIKAFTA (elexacaftor / tezacaftor / ivacaftor) Tablets is approved for the same indication but for patients 6 years of age and older. This NDA is proposing to expand the pediatric population down to 2 years of age with a different dosage form, oral granules.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by January 13, 2023. The resubmitted PI will be used for further labeling review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

NO 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *The HL section is beyond one-half page. Please submit a waiver and request that a waiver be granted for the length of the HL to be longer than one-half page for the combined labeling of NDA 217660 Trikafta Oral Granules with NDA 212273 Trikafta Tablets.*

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required

Selected Requirements of Prescribing Information

• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment: *Should the dosage forms (Tablets and Oral Granules) be placed outside of the paraentheses separte from established name?*

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.****"*)

Comment:

Recent Major Changes (RMC) in Highlights

YES 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment: *Althought RMC in HL does not apply to new NDA approvals, because NDA 217660 will have combined labeling with NDA 212273, we will retain the RMC in HL section.*

YES 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment: *Currently there is a placeholder for the date and applicant will need to include the final revision date.*

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

NO 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment: *This combined labeling will include two dosage forms, tablets and oral granules, and although the information is not presented in bulleted headings, it is presented in a tabular*

format which enhances the accessibility of information. This tabular format is acceptable and we will not ask the applicant to revise the format.

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment: *Currently there is a placeholder for the date and applicant will need to include the final revision date.*

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*."

Comment:

YES 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

YES 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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/

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