CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211358Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

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:	July 18, 2018
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 211358
Product Name and Strength:	Orkambi (lumacaftor/ivacaftor) oral granules, 100 mg/125 mg and 150 mg/188 mg
Applicant/Sponsor Name:	Vertex Pharmaceuticals Inc.
FDA Received Date:	July 13, 2018
OSE RCM #:	2018-400-1
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the revised container labels, carton and wallet card labeling, Prescribing Information (PI), and Patient Information for Orkambi (lumacaftor/ivacaftor) oral granules, NDA 211358, (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] We agree with the proposed changes, find Vertex's rational acceptable, and have consulted with CMC.

2 CONCLUSION

We have no additional recommendations at this time.

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[a] Patel, M. Label and Labeling Review for ORKAMBI (lumacaftor/ivacaftor) (NDA 211358). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 19. RCM No.: 2018-400.

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/s/

MADHURI R PATEL
07/18/2018

SARAH K VEE
07/18/2018

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

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

Memorandum

Date: July 16, 2018

To: Christine Ford
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Kyle Snyder, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Pharm.D.
Team Leader, OPDP

Subject: OPDP Labeling Comments for ORKAMBI® (lumacaftor/ivacaftor) oral granules

NDA: 211358

In response to DPARP's consult request dated March 6, 2018, OPDP has reviewed the proposed prescribing information (PI), patient package insert (PPI), and carton and container labeling for ORKAMBI® (lumacaftor/ivacaftor) oral granules.

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DPARP on July 5, 2018. Comments on the proposed PI are provided below.

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

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on July 13, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Kyle Snyder at (240) 402-8792 or kyle.snyder@fda.hhs.gov.

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/s/

KYLE SNYDER
07/16/2018

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:	July 13, 2018
To:	Sally Seymour M.D. Acting Director **Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Kyle Snyder, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	ORKAMBI (lumacaftor/ivacaftor)
Dosage Form and Route:	oral granules
Application Type/Number:	NDA 211358
Applicant:	Vertex Pharmaceuticals Incorporated

1 INTRODUCTION

On February 7, 2018, Vertex Pharmaceuticals Incorporated submitted for the Agency's review a 505(b) non-New Molecular Entity (non-NME) New Drug Application (NDA) 211358 for ORKAMBI (lumacaftor/ivacaftor) oral granules. The proposed indication for ORKAMBI (lumacaftor/ivacaftor) oral granules is the treatment of cystic fibrosis (CF) in patients 2 years and older, homozygous for the *F508del-CFTR* mutation in the CFTR gene.

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 Pulmonary, Allergy, and Rheumatology Products (DPARP) on March 6, 2018 for DMPP and OPDP to review the Applicant's propose Patient Package Insert (PPI) for ORKAMBI (lumacaftor/ivacaftor) oral granules.

2 MATERIAL REVIEWED

- Draft ORKAMBI (lumacaftor/ivacaftor) PPI received on February 7, 2018, and received by DMPP and OPDP on July 6, 2018.
- Draft ORKAMBI (lumacaftor/ivacaftor) Prescribing Information (PI) received on February 7, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 6, 2018.

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%. A reading ease score of 60% corresponds to an 8th grade reading level.

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.

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)

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 is 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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/s/

KELLY D JACKSON
07/13/2018

KYLE SNYDER
07/13/2018

SHARON W WILLIAMS
07/13/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

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:	June 19, 2018
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 211358
Product Name and Strength:	Orkambi (lumacaftor/ivacaftor) oral granules, 100 mg/125 mg and 150 mg/188 mg
Product Type:	Multi-ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Vertex Pharmaceuticals Inc.
FDA Received Date:	February 7, 2018
OSE RCM #:	2018-400
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 REASON FOR REVIEW

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the proposed container labels, carton and wallet card labeling, Prescribing Information (PI), and Patient Information for Orkambi (lumacaftor/ivacaftor) oral granules, NDA 211358, submitted by Vertex Pharmaceuticals Inc. on February 7, 2018 to determine if it is acceptable from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material 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
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Orkambi (lumacaftor/ivacaftor) tablet (NDA 206038) was approved on July 2, 2015 for the treatment of cystic fibrosis (CF) in patients age 6 years and older who are homozygous for the F508del mutation in the CFTR gene. On February 7, 2018, the Applicant submitted NDA 311358, which proposes lumacaftor and ivacaftor oral granules for ages 2 through 5 years of age. We note the PI, Patient Information, container labels, and carton/wallet labeling can be improved for clarity and to facilitate product identification of the product. Additionally, we note that the wallet cards and Patient Information can be improved to provide clarity on the how to prepare the product.

4 CONCLUSION & RECOMMENDATIONS

We note that the container label and carton labeling can be improved to enhance important information and facilitate identification of the product. We also note that the PI and Patient Information can be improved to mitigate dose confusion.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI) and Patient Information

1. We recommend using only metric measurements [e.g., “5 mL” instead of “one teaspoon (5 mL)” or “1 teaspoon”] throughout the PI and Patient Information where appropriate to prevent medication errors.
2. Consider using the same dosing table in the dosage & administration section of the highlights of prescribing information as that of Section 2.1 from the full PI for consistency and ease of reading of the information.

4.2 RECOMMENDATIONS FOR VERTEX PHARMACEUTICALS INC.

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

A. General Comments for all labeling

1. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2). Also, ensure that the established name is at least half the size of the proprietary name to be in accordance with 21 CFR 201.10(g)(2).
2. For each instance of “packet”, revise to state “unit dose packet” for consistency with the prescribing information.
3. Each package configuration should have unique NDC numbers. Additionally, NDC numbers across the Orkambi product lines are similar (i.e. middle digits differ only by one digit (51167-X00-02)). The similarity of the product code numbers has led to wrong drug, strength selection, and dispensing errors. The middle digits of the NDC number are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, the assignment of similar numbers for the middle digits is not an effective differentiating feature. Revise the product code in the NDC numbers to ensure that the middle digits are not similar across Orkambi product lines. If the middle digits cannot be revised, increase the prominence of the middle digits by increasing their size in comparison to the remaining digits in the NDC number and/or put them in bold type. For example: XXXX-**XXX**-XX.
4. We did not identify a placeholder (“LOT” or “EXP”) for the lot number and expiration date on the proposed labels and labeling. Ensure that the lot number and expiration date are presented in accordance with 21 CFR 201.10(i) and 21 CFR 201.17, and that they are clearly differentiated from one another.[1] Ensure that the lot number and expiration date are not located in close proximity to other numbers where the numbers can be mistaken as the lot number or expiration date.[2] To minimize confusion and reduce the risk for deteriorated

[1] Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert Acute Care. 2014;19(23):1-4.

[2] Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

drug medication errors, identify the format for the expiration date you intend to use (see below for examples):

   a. DDMMMYYYY (e.g., 31JAN2013)
   b. MMMYYYY (e.g., JAN2013)
   c. YYYY-MMM-DD (e.g., 2013-JAN-31)
   d. YYYY-MM-DD (e.g., 2013-01-31)

B. Container Labels
   1. The linear barcode should be surrounded by sufficient white space to allow scanners to read the barcode properly in accordance with 21 CFR 201.25(c)(1)(i).

C. Wallet Card Labeling
   1. Add the statement “per unit-dose packet” after the strength in the colored circle on the principal display panel to mitigate the risk of strength confusion between each unit dose packet and the contents of the wallet card.
   2. We note the wallet card labeling does not have a linear barcode. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product’s linear barcode to each individual wallet as required per 21CFR 201.25(c)(2).
   3. We recommend using only metric measurements [e.g., “5 mL” instead of “one teaspoon (5 mL)] where appropriate to prevent medication errors.
   4. Consider adding storage information for the wallet cards.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Orkambi oral granules received on February 7, 2018 from Vertex Pharmaceuticals Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Orkambi oral granules and the Listed Drug

Product Name	**Orkambi**	**Orkambi**
Initial Approval Date	N/A	July 2, 2015
Active Ingredient	lumacaftor and ivacaftor	lumacaftor and ivacaftor
Indication	treatment of cystic fibrosis (CF) in patients age 2 years through 5 years who are homozygous for the F508del mutation in the CFTR gene.	treatment of cystic fibrosis (CF) in patients age 6 years and older who are homozygous for the F508del mutation in the CFTR gene.
Route of Administration	oral	oral
Dosage Form	oral granules	tablet
Strength	100 mg/125 mg and 150 mg/188 mg	100 mg/125 mg and 200 mg/125 mg
Dose and Frequency	• Less than 14 kg: 1 packet of 100 mg/125 mg lumacaftor/ivacaftor every 12 hours (total daily dose: lumacaftor 200 mg/ivacaftor 250 mg) • 14 kg or greater: 1 packet of 150 mg/188 mg lumacaftor/ivacaftor every 12 hours (total daily dose: lumacaftor 300 mg/ivacaftor 376 mg)	• Ages 6 through 11 years: 2 lumacaftor 100 mg/ivacaftor 125 mg tablets every 12 hours (total daily dose: lumacaftor 400 mg/ivacaftor 500 mg) • Ages 12 years and older: 2 lumacaftor 200 mg/ivacaftor 125 mg tablets every 12 hours (total daily dose: lumacaftor 800 mg/ivacaftor 500 mg)
How Supplied	carton contains 4 individual wallets. Wallets contain 14 unit-dose packets. 56 count	112–count tablet box containing a 4-week supply (4 weekly cartons of 7 daily blister strips with 4 tablets per strip)
Storage	20°C -25°C (68°F -77°F) with excursions permitted to 15°C-30°C (59-86°F)	20°C -25°C (68°F -77°F) with excursions permitted to 15°C-30°C (59-86°F)
Container Closure	n/a	n/a

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 24, 2018, we searched DMEPA's previous reviews using the terms, 'orkambi'. Our search identified 5 previous label and labeling and postmarketing reviews[a,b,c,d ,e f], and we confirmed that our previous recommendations were implemented or considered.

APPENDIX C. HUMAN FACTORS STUDY – N/A

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On April 24, 2018, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care Community Nursing Long-Term Care Canada Safety Bulletin Pennsylvania Patient Safety Advisory
Search Strategy and Terms	Match Exact Word or Phrase: orkambi

D.2 Results

No article was retrieved from the above search.

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[a] McMillan, T. Label and Labeling Review for Orkambi (NDA 206038/S-007). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 DEC 21. RCM No.: 2017-889

[b] Owens, L. Label and Labeling Review for Orkambi (NDA 206038/S-005). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 AUG 2. RCM No.: 2016-970

[c] Owens, L. Label and Labeling Review for Orkambi (NDA 206038/S-006). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JUL 5. RCM No.: 2016-1137

[d] Owens, L. Medication Error Review for Orkambi NDA 206038. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 MAR 28. RCM No.: 2016-436

[e] Owens, L. Label and Labeling Review for Orkambi (NDA 206038/S-001). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 MAR 27. RCM No.: 2016-603

[f] Owens, L. Label and Labeling Review for Orkambi NDA 206038. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 MAY 28. RCM No.: 2014-2321

APPENDIX F. OTHER – N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error data, we reviewed the following Orkambi oral granules labels and labeling submitted by Vertex Pharmaceuticals Inc.

- Container label received on February 7, 2018
- Carton labeling received on February 7, 2018
- Wallet Labeling received on February 7, 2018
- Patient Information received on February 7, 2018
- Prescribing Information (Image not shown) received on February 7, 2018

G.2 Label and Labeling Images

Container Labels

(b) (4)

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

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/s/

MADHURI R PATEL
06/19/2018

SARAH K VEE
06/19/2018

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 6/1/2018

TO: Division of Pulmonary, Allergy and Rheumatology Products
Office of Drug Evaluation II

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 211358

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	(b) (4)

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/s/

SHILA S NKAH
06/01/2018