CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212436Orig1s000

OTHER REVIEW(S)

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:	October 25, 2019
To:	Julia Beaver, MD Director **Division of Oncology Products 1 (DOP1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Addendum to Patient Labeling Review dated August 22, 2019: Patient Package Insert (PPI)
Drug Name (established name):	IBRANCE (palbociclib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	212436
Applicant:	Pfizer, Inc.

1 INTRODUCTION

On January 31, 2019, Pfizer, Inc. submitted for the Agency's review an original New Drug Application (NDA) 212436 for IBRANCE (palbociclib) tablets.

To note, the Applicant has a currently approved product, IBRANCE (palbociclib) capsules (NDA 207103) on the market. IBRANCE (palbociclib) capsules was approved on February 03, 2015. This NDA seeks full approval for IBRANCE (palbociclib) proposed tablet formulation for oral use in the currently marketed indications. The new tablet formulation will allow administration of palbociclib with or without food and concomitant administration of proton pump inhibitors (PPIs) under any food intake condition. The currently marketed capsule formulation is labeled to be administered with food to reduce variability in drug absorption and to mitigate drug-drug-interactions (DDIs) with gastric acid reducing agents (local antacids, H2-receptor antagonists [H2RAs], and PPIs).

This amended review replaces the review completed by DMPP-OPDP on August 22, 2019 which includes the addition of patient-friendly language in the PPI under the "What is the most important information I should know about IBRANCE?" section for consistency with section "5.2 Interstitial Lung Disease (ILD)/Pneumonitis" of the PI and the "What is IBRANCE?" section for consistency with section "1 INDICATIONS AND USAGE" of the PI.

Please let us know if you have any questions.

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/s/

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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:	October 25, 2019
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	NDA 212436
Product Name and Strength:	Ibrance (palbociclib) tablets, 75 mg, 100 mg, and 125 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Pfizer Inc.
FDA Received Date:	January 31, 2019, September 20, 2019, and October 9, 2019
OSE RCM #:	2019-311
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of the review process for Ibrance (palbociclib) tablets, the Division of Oncology Products 1 (DOP1) requested that we review the proposed Ibrance prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

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 – N/A
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 or ISMP Newsletters 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

Ibrance was approved in 2015, and is currently marketed as immediate release capsules with strengths of 75 mg, 100 mg, and 125 mg. Pfizer proposed the tablet formulation to improve drug product dissolution and improve drug absorption over the currently marketed Ibrance capsules and to reduce the drug-drug interactions with gastric acid-reducing agents that were observed with the currently approved capsules formulation.[a] Unlike the currently marketed capsules, which must be taken with food, the proposed tablet formulation may be administered with or without food and is bioequivalent to the currently approved capsule formulation.

Pfizer plans to (b) (4)
(b) (4)

[a] 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods: Palbociclib (PD-0332991). New York (NY): Pfizer Inc. 2019 Jan 31. Available from: \\cdsesub1\evsprod\nda212436\0001\m2\27-clin-sum\summary-biopharm.pdf.

(b) (4)

The proposed Ibrance tablets have the same strength, 75 mg, 100 mg, and 125 mg, and have the same indication and recommended dosage as the currently marketed Ibrance capsules. Furthermore, the presentation of the Ibrance tablets in blister packs will provide adequate differentiation between Ibrance tablets and Ibrance capsules, which are available in bottles configuration. We did not identify any new risks of confusion with the proposed Ibrance tablets product since the Ibrance tablets are substitutable with the currently marketed Ibrance capsules.

3.1 PRESCRIBING INFORMATION (PI)

We reviewed Section 2 Dosage and Administration, Section 3 Dosage Forms and Strengths, Section 16 How Supplied/Storage and Handling, and Section 17 Patient Counseling Information, and find the proposed changes acceptable from a medication error perspective.

3.2 CONTAINER LABEL AND CARTON LABELING

Pfizer submitted the Ibrance container label and carton labeling for two types of blister pack packaging configuration: (1) wallet card and (2) dose pack. On July 31, 2019, Pfizer confirmed that the commercial packaging will only be the wallet card configuration. Thus, we limited our review to the container label and carton labeling for the wallet card configuration only.[d]

We noted that the proposed container label and carton labeling for the blister packs for the Ibrance tablets share the same color strength differentiation as the capsules (e.g., (b) (4) for 75 mg, (b) (4) for 100 mg, and (b) (4) for 125 mg). Therefore, we determined that there is sufficient color differentiation between the different strengths, and the use of the same colors on labels and labeling may help in transition to Ibrance tablets from capsules for patients already taking Ibrance capsules.

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[b] Type B Briefing Document. Ibrance (Palbociclib) Tablets. Pre-NDA Type B Meeting. 13 August 2018. New York (NY): Pfizer Inc. 2018 Aug 21. Available from: \\cdsesub1\evsprod\ind069324\0863\m1\us\pre-nda-meeting-document.pdf.

[c] Tilley, A. IND 069324. Meeting Preliminary Comments. Silver Spring (MD): FDA, CDER, OND, OHOP, DOP1 (US); 2018 Sept 12.

[d] NDA 212436 for IBRANCE (palbociclib) Tablets. Response to Information Request (23 July 2019). New York (NY): Pfizer Inc. 2019 July 31. Available from: \\cdsesub1\evsprod\nda212436\0009\m1\us\response-23jul19-ir-query8-9.pdf

However, we determined that the proposed container label and carton labeling for the blister packs may be improved to ensure safe product use. DOP1 communicated our recommendations below to Pfizer on September 24, 2019.[e]

A. General Comments (Container labels & Carton Labeling)

1. We recommend including the product strength as per tablet to clearly indicate that XX mg is in each tablet and to prevent confusion that XX mg is the total contents of the entire blister pack. We recommend revising the strength statement as follows: "XX mg per tablet" or "XX mg/tablet" on the principal display panel.
2. Consider revising the administration instruction (b) (4) to assertive language and to include the number of tablets to be taken once daily for 21 consecutive days. For example: "Take 1 tablet once daily for 21 consecutive days followed by 7 days off treatment". This will clarify that patients should only take 1 tablet once daily.
3. We noted that the instructions for "How should I take IBRANCE® (palbociclib)?" contain the same instructions in the "How should I take IBRANCE?" section of the Patient Package Insert (PPI). Therefore, we recommend you ensure that the instructions in the blister pack match the instructions in the final approved PPI.

B. Carton Labeling

1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the 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. See *Draft Guidance: Product Identifiers Under the Drug Supply Chain Security Act-Questions and Answers*, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers.

Pfizer submitted revised Ibrance container labels and carton labeling on October 9, 2018 in response to our recommendations above. We reviewed the October 9, 2018 Ibrance container

[e] The following recommendations were communicated to Pfizer on Septmber 24, 2019 in Robertson, K. "RE: NDA 212436; Ibrance Label Query" Message to Elizabeth VanAlphen. Silver Spring (MD): FDA, CDER, OND, DOP1 (US); 2019 Sept 24.

labels and carton labeling and noted that Pfizer implemented all of our recommendations except one recommendation regarding to the strength per tablet. Pfizer added the product strength per tablet on the bottom of the container label and carton labeling. However, Pfizer stated they did not change the bolded colored dose strength text on both the carton Labeling and the container labels (Wallet Card) to remain consistent with the Pfizer standard trade dress for packaged product along with consistency with the current dosage strength text used on the bottle label for Ibrance Capsules.[f] Furthermore, Pfizer stated that the expiration date format is "MM/YYYY" and will consider "YYYY-MM" format in a future implementation.[f]

While we find the proposed alternative expiration date format acceptable, we find the proposed change to the strength unacceptable because the strength statement for a blister pack should be expressed as "XX mg per tablet" or "XX mg/tablet" to prevent the risk of medication errors. At the same time, we acknowledge the approaching application action date and this outstanding labeling issue does not rise to the level of a complete response. Therefore, we recommend revising the strength expression on the container labels and carton labeling at the next printing.

4 CONCLUSION & RECOMMENDATIONS

The proposed Ibrance PI received on January 31, 2019 is acceptable from a medication error perspective. The proposed container label and carton labeling for the blister packs may be improved to ensure safe product use. We provide specific recommendations in Section 4.1 below.

4.1 RECOMMENDATIONS FOR PFIZER INC.

We recommend the following be implemented at next printing:

A. General Comments (Container labels & Carton Labeling)

1. Revise the strength statement that immediately follows the established name to "XX mg per tablet" or "XX mg/tablet" so that the strength statement clearly indicate that XX mg is in each tablet and to prevent the risk of medication error associated with confusion that XX mg is the total contents of the entire blister pack. We acknowledge that Ibrance capsules container labels use "XX mg" instead of "XX mg per tablet". However, because the proposed Ibrance tablets are packaged in a blister containing 7 tablets, there is risk that patients may think they need to take all 7 tablets to achieve the "XX mg" strength. This risk is unique to the proposed blister pack container closure. See draft *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, available at https://www.fda.gov/regulatory-

[f] IBRANCE (palbociclib) tablets. NDA 212436. Response to Information Request – 24 Sep 2019. New York (NY): Pfizer Inc. 2019 Oct 9. Available from: \\cdsesub1\evsprod\nda212436\0012\m1\us\response-24sep19-labeling.pdf

information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ibrance tablets received on September 20, 2019 from Pfizer Inc., and Ibrance capsules retrieved from the September 9, 2019 approved Ibrance capsules Prescribing Information[g].

Table 2. Product Information for the currently marketed Ibrance capsules and proposed Ibrance tablets

Product Name	**Ibrance capsule** NDA 207103	**Ibrance tablet** NDA 212436
Initial Approval Date	February 3, 2015	N/A
Active Ingredient	palbociclib	palbociclib
Indication	treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with: • an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or in men; or • fulvestrant in patients with disease progression following endocrine therapy	
Route of Administration	Oral	Oral
Dosage Form	**Capsules**	**Tablets**
Strength	75 mg, 100 mg, and 125 mg	75 mg, 100 mg, and 125 mg
Dose and Frequency	Recommended starting dose: 125 mg once daily taken with or without food for 21 days followed by 7 days off treatment. **Recommended Dose Modification for Adverse Reactions** Recommended starting dose: 125 mg/day First dose reduction: 100 mg/day Second dose reduction: 75 mg/day* *If further dose reduction below 75 mg/day is required, discontinue.	
Administration	**Taken with food**	**Taken with or without food**
How Supplied	Bottle of 21 capsules	Monthly box containing 3 weekly blister packs of 7 tablets each (21 tablets total)
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F)	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). **Store in the original blister pack.**
Container Closure	60 cc (b) (4) (b) (4) bottle	packed in a (b) (4) (b) (4) blister (b) (4)

[g] Ibrance [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 Sept 9. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207103s012lbl.pdf.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 17, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, Ibrance. Our search identified 2 previous reviews[h,i], and we considered our previous recommendations to see if they are applicable for this current review.

[h] Gao, T. Label and Labeling Review for Ibrance (NDA 207103/S-005). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 June 2. RCM No.: 2017-736.

[i] Mathew, D. Label and Labeling Review for Ibrance (NDA 207103). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 Jan 12. RCM No.: 2014-1280.

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,[j] along with postmarket medication error data, we reviewed the following Ibrance labels and labeling submitted by Pfizer Inc.

- Container labels
- Revised container labels received October 9, 2019
- Carton labeling received on January 31, 2019
- Revised carton labeling received October 9, 2019
- Container label for professional samples received on January 31, 2019
- Revised container label for professional samples received on October 9, 2019
- Carton labeling for professional samples received on January 31, 2019
- Revised carton labeling for professional samples received on October 9, 2019
- Prescribing Information (Image not shown) received on September 20, 2019, available from \\cdsesub1\evsprod\nda212436\0011\m1\us\lab-1371-0-4-lab-1372-0-3-annotated.doc

Due to the numerous container label and carton labeling for all three strengths (75 mg, 100 mg, and 125 mg), only the container labels and carton labeling for the 75 mg strength are included below. The 75 mg strength is representative of the container label and carton labeling for all three strengths. See submission for container labels and carton labeling for other strengths.

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

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

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

Memorandum

Date: August 29, 2019

To: Preeti Narayan, MD, Clinical Reviewer
Division of Oncology Products (DOP-1)

Kimberly Robertson, Regulatory Project Manager, DOP-1

William Pierce, PharmD, Associate Director for Labeling, DOP-1

From: Maritsa Serlemitsos-Day, PharmD, BCPS, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kevin Wright, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for **IBRANCE® (palbociclib) tablets, for oral use**

NDA: 212436

In response to DOP-1's consult request dated May 8, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for IBRANCE® (palbociclib) tablets, for oral use (Ibrance). This application proposes a tablet formulation of palbociclib and seeks approval of all indications approved under NDA 207103.

OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DOP-1 (Sherry Hou) on August 15, 2019, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on August 22, 2019.

OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on January 31, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Maritsa Serlemitsos-Day at (301) 796-1760 or maritsa.serlemitsos-day@fda.hhs.gov.

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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:	August 22, 2019
To:	Julia Beaver, MD Director **Division of Oncology Products 1 (DOP1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Maritsa Serlemitsos-Day, PharmD, BCPS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
From:	Morgan Walker, PharmD, MBA, CPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	IBRANCE (palbociclib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 212436
Applicant:	Pfizer, Inc.

1 INTRODUCTION

On January 31, 2019, Pfizer, Inc. submitted for the Agency's review an original New Drug Application (NDA) 212436 for IBRANCE (palbociclib) tablets.

To note, the Applicant has a currently approved product, IBRANCE (palbociclib) capsules (NDA 207103) on the market. IBRANCE (palbociclib) capsules was approved on February 03, 2015. This NDA seeks full approval for IBRANCE (palbociclib) proposed tablet formulation for oral use in the currently marketed indications. The new tablet formulation will allow administration of palbociclib with or without food and concomitant administration of proton pump inhibitors (PPIs) under any food intake condition. The currently marketed capsule formulation is labeled to be administered with food to reduce variability in drug absorption and to mitigate drug-drug-interactions (DDIs) with gastric acid reducing agents (local antacids, H2-receptor antagonists [H2RAs], and PPIs).

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 Oncology Products 1 (DOP 1) on April 11, 2019 and revised on May 8, 2019, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI for IBRANCE (palbociclib) tablets.

2 MATERIAL REVIEWED

- Draft IBRANCE (palbociclib) tablets PPI received on January 31, 2019, and received by DMPP and OPDP on August 15, 2019.
- Draft IBRANCE (palbociclib) tablets Prescribing Information (PI) received on January 31, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 15, 2019.

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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