CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208855Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: **February 7, 2018**

To: Julia Beaver, M.D., Acting Director
Division of Oncology Products 1 (DOP1)

Janice Kim, PharmD, Regulatory Project Manager, (DOP1)

William Pierce, PharmD, Associate Director for Labeling, (DOP1)

From: Kevin Wright, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Brian Tran, PharmD, MBA, Team Leader, OPDP

Subject: OPDP Labeling Comments for Verzenio™ (abemaciclib) tablets, for oral use

NDA: 208855

In response to DOP1's consult request dated October 4, 2017, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton labeling for the original NDA submission for Verzenio™ (abemaciclib) tablets, for oral use (Verzenio).

OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DOP1 (Janice Kim) on January 30, 2018, 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 February 6, 2018.

OPDP reviewed the proposed blister card label and carton labeling submitted by the Sponsor to the electronic document room under NDA 208716 on September 1, 2017, and was completed on September 1, 2017.

Thank you for your consult. If you have any questions, please contact Kevin Wright at (301) 796-3621 or kevin.wright@fda.hhs.gov.

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/s/

KEVIN WRIGHT
02/07/2018

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:	February 6, 2018
To:	Julia Beaver, MD Acting 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:	Shawna Hutchins, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Kevin Wright, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	VERZENIO (abemaciclib)
Dosage Form and Route:	Tablets, for oral use
Application Type/Number:	NDA 208855
Applicant:	Eli Lilly and Company

1 INTRODUCTION

On August 15, 2017, Eli Lilly and Company, submitted for the Agency's review an original New Drug Application (NDA 208855) seeking approval for the use of abemaciclib, tablets, for oral use, in combination with aromatase inhibitors for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) metastatic breast cancer in women as initial endocrine-based therapy and to expand the use of abemaciclib in combination with fulvestrant to include "(b) (4)" also in HR+, HER2- metastatic breast cancer.

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 (DOP1) on October 4, 2017, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for abemaciclib, tablets, for oral use.

2 MATERIAL REVIEWED

- Draft VERZENIO (abemaciclib) PPI received on August 15, 2017, revised by the review division during the review cycle, and received by DMPP and OPDP on January 30, 2018.
- Draft VERZENIO (abemaciclib) Prescribing Information (PI) received on September 15, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 30, 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. 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

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/

SHAWNA L HUTCHINS
02/06/2018

KEVIN WRIGHT
02/06/2018

LASHAWN M GRIFFITHS
02/06/2018

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:	January 17, 2018
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	NDA 208855
Product Name and Strength:	Verzenio (Abemaciclib) Tablets, 50 mg, 100 mg, 150 mg, 200 mg
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Eli Lilly and Company (Eli Lilly)
Submission Date:	January 17, 2018
OSE RCM #:	2017-1683
DMEPA Safety Evaluator:	Grace P. Jones, PharmD, BCPS
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As part of the NDA 208855 review for Verzenio (abemaciclib) tablets, the Division of Oncology Products 1 (DOP1) requested that we review the proposed Verzenio Prescribing Information (PI) to identify areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND INFORMATION

Verzenio (abemaciclib) tablets, 50 mg, 100 mg, 150 mg, and 200 mg, was approved on September 28, 2017 under NDA 208716 for the treatment of HR+, HER2- advanced or metastatic breast cancer as a single agent following endocrine therapy and (b) (4) prior chemotherapy, or in combination with fulvestrant following endocrine therapy. The Applicant submitted NDA 208855 for Verzenio (abemaciclib) tablets on August 15, 2017 for the newly proposed indication: treatment of postmenopausal women with HR+, HER2- advanced or metastatic breast cancer in combination with aromatase inhibitor as initial endocrine-based therapy.

Based on email correspondence from DOP1[a], there is no newly proposed container labels and carton labeling for NDA 208855 because the same strength tablets packaged in 7-day dose packs already approved under NDA 208716 will be used for this NDA 208855.

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	N/A
ISMP Newsletters	N/A
FDA Adverse Event Reporting System (FAERS)*	E
Other	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

[a] Email correspondence dated November 14, 2017.

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed Section 2 Dosage and Administration of the Verzenio PI and noted addition of using Verzenio in combination with aromatase inhibitor information for the newly proposed indication. There are no other proposed changes to the recommended dosage and administration. Additionally, there are no changes to the proposed Verzenio PI Section 3 Dosage Forms and Strengths and Section 16 How Supplied/Storage and Handling. Thus, the proposed Verzenio PI appears acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

The proposed Verzenio prescribing information (PI) for Verzenio is acceptable from a medication error perspective. We have no further recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Verzenio that Eli Lilly submitted on January 17, 2018. Newly proposed information in NDA 208855 are highlighted.

Table 2. Relevant Product Information for Verzenio	
Initial Approval Date	N/A
Active Ingredient	Abemaciclib
Indication	Indicated: • in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. • in combination with fulvestrant (b) (4) for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy. • as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.
Route of Administration	Oral
Dosage Form	Tablets
Strength	50 mg, 100 mg, 150 mg, 200 mg
Dose and Frequency	• When used in combination with fulvestrant or aromatase inhibitor, the recommended dose of VERZENIO is 150 mg taken orally twice daily. • When used as monotherapy, the recommended dose of VERZENIO is 200 mg taken orally twice daily.
How Supplied	7-day dose packs as: 200 mg dose (one 200 mg tablet), 14 tablets 150 mg dose (one 150 mg tablet), 14 tablets 100 mg dose (one 100 mg tablet), 14 tablets 50 mg dose (one 50 mg tablet), 14 tablets
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Container Closure	Packaged in a blister presentation using a (b) (4) [redacted]

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 4, 2018, we searched DMEPA's previous reviews using the terms, Verzenio. Our search identified two previous labels and labeling reviews for Verzenio (abemaciclib) tablets,[b,c] and we confirmed that our previous recommendations were implemented or considered.

[b] Jones G. Label and Labeling Review for Verzenio NDA 208716. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); Insert Date As 2017 SEP 21. RCM No.: 2017-947-1.

[c] Jones G. Label and Labeling Review for Verzenio NDA 208716. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); Insert Date As 2017 JUL 25. RCM No.: 2017-947.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

On January 4, 2018, we searched FAERS using the criteria in the table below and identified one case. We individually reviewed the case, and limited our analysis to instances 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.[d] We excluded the case because it described adverse drug reaction, which led to missed doses.

Criteria Used to Search FAERS	
Initial FDA Receive Dates:	None
Product Name:	Verzenio
Product Active Ingredient (PAI):	abemaciclib
Event:	SMQ *Medication errors* (Narrow)
Country (Derived):	USA

E.2 Results

Our search identified one case, which did not describe an error relevant for this review.

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

[d] 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.

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,[e] along with postmarket medication error data, we reviewed the following Verzenio labels and labeling submitted by Eli Lilly on January 17, 2018.

- Prescribing Information (Image not shown)

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

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/s/

GRACE JONES
01/17/2018

CHI-MING TU
01/17/2018

Clinical Inspection Summary

Date	December 27, 2017
From	Lauren Iacono-Connors, Ph.D., Reviewer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Division of Clinical Compliance Evaluation
To	Janice Kim, Regulatory Project Manager Lynn Howie, Clinical Reviewer Division of Oncology Products 1
NDA #	208855
Applicant	Eli Lilly and Company
Drug	Verzenio™ (abemaciclib)
NME	Yes
Therapeutic Classification	Cyclin-dependent Kinase (CDK) Inhibitor
Proposed Indication	Metastatic breast cancer
Consultation Request Date	October 4, 2017 (NDA submission date: August 15, 2017)
Summary Goal Date	February 1, 2018
Action Goal Date	April 13, 2018
PDUFA Date	April 15, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study I3Y-MC-JPBM was submitted to the Agency in support of NDA 208855. Three clinical sites, Dr. Mario Campone, M.D. (Site 356), Dr. Orit Freedman, M.D. (Site 203), Dr. Shani Paluch-Shimon (754), and one CRO, (b) (4) were selected for audit.

There were no significant inspectional findings for clinical investigators Dr. Mario Campone, Dr. Orit Freedman, Dr. Shani Paluch-Shimon and the CRO (b) (4) The data from Study I3Y-MC-JPBM submitted to the Agency in support of NDA 208855, appear reliable based on available information.

II. BACKGROUND

Eli Lilly and Company (Lilly) seeks approval to market abemaciclib for the treatment of postmenopausal women with HR+, HER2- (b) (4) metastatic breast cancer (b) (4) The key study supporting this application is Study I3Y-MC-JPBM (MONARCH 3).

The following overview of the Study I3Y-MC-JPBM is intended as background context for interpreting the inspectional findings.

The study was conducted at 158 clinical centers in 22 countries. A total of 493 subjects (328 abemaciclib + NSAI; 165 placebo + NSAI) were randomized into Study I3Y-MC-JPBM. Of those, 488 subjects (327 abemaciclib + NSAI; 161 placebo + NSAI) received at least 1 dose of study treatment. The study was conducted under IND 106100.

Study I3Y-MC-JPBM is entitled, "A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Nonsteroidal Aromatase Inhibitors (Anastrozole or Letrozole) plus LY2835219, a CDK4/6 Inhibitor, or Placebo in Postmenopausal Women with Hormone Receptor-Positive, HER2-Negative Locoregionally Recurrent or Metastatic Breast Cancer with No Prior Systemic Therapy in this Disease Setting."

Study Period: Date of first subject enrolled: November 18, 2014
Data cut-off date for analysis: January 31, 2017

Primary efficacy endpoint: Progression Free Survival (PFS) per RECIST 1.1., as determined by the clinical investigator. PFS is defined as the time from randomization to the earlier of disease progression per RECIST v1.1 or death due to any cause.

In addition, a blinded central review of the radiographic images per RECIST v1.1 was conducted by an Independent Radiology Committee (IRC).

Objectives of Inspections:

a. Verify PFS as determined by the clinical investigators
b. Verify PFS as determined by an independent review committee (IRC)
c. Verify OS
d. Identification, documentation, and reporting of adverse events (AEs)
e. General compliance with the investigational plan.

III. RESULTS (by site):

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
CI #1: Mario Campone, M.D. (Site 356) Bd Jacques Monod Saint Herblain Cedex, 44805 France	Protocol: I3Y-MC-JPBM Subjects: 14	December 18 – 22, 2017	*NAI
CI #2: Orit Freedman, M.D. (Site 203) R. S. McLaughlin Durham, Regional Cancer Centre One Hospital Court Oshawa, Ontario Canada	Protocol: I3Y-MC-JPBM Subjects: 8	December 18 – 21, 2017	*NAI

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
CI #3: Shani Paluch-Shimon, M.D. **(Site 754)** 2 Sheba Road Tel Hashomer Ramat Gan, Israel 5266202 Israel	Protocol: I3Y-MC-JPBM Subjects: 10	December 10-12, 2017	*NAI
CRO: Performed as the Independent Review Committee (IRC) for Image Assessment (b) (4)	Protocol: I3Y-MC-JPBM Randomly selected subjects: 26	October 10-12, 2017	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Dr. Mario Campone, M.D. (Site 356)

Dr. Mario Campone was the CI for what ended up being two separate clinical site locations: one located in St. Herblain, France and the other located in Angers, France. Each site used different study coordinators, pharmacy, delegation logs, radiologists, Sub-investigators, ect. Both site locations were inspected. The information provided below is a combined summary for both site locations.

The site screened 19 subjects and enrolled 14 subjects. A record review was done for all subjects. At the time of this inspection seven subjects were still on study. The inspection included review of all subject records including eCRFs, electronic medical histories including the radiology scans, and study specific hard copy folders containing inclusion/exclusion records, randomization confirmations, informed consent documentation, adverse and serious adverse events (SAE) documentation, correspondence, laboratory reports, and target lesion measurements obtained from the radiology scans. The source data was compared to the data listings submitted to the application.

The inspection revealed no significant deficiencies. The primary efficacy endpoint data were verifiable with the source records maintained at the site. There was no evidence of under-reporting of AEs.

2. Dr. Orit Freedman, M.D. (Site 203)

The site screened nine subjects and enrolled eight subjects. A record review was done for all eight enrolled subjects. The inspection included review of all subject records including eCRFs, electronic medical histories including the radiology scans, and study specific hard copy folders containing inclusion/exclusion records, randomization confirmations, informed consent documentation, adverse and serious adverse events (SAE) documentation, correspondence, laboratory reports, and target lesion measurements obtained from the radiology scans. The source data was compared to the data listings submitted to the application.

The inspection revealed no significant deficiencies. The primary efficacy endpoint data were verifiable with the source records maintained at the site. There was no evidence of under-reporting of AEs.

3. Dr. Shani Paluch-Shimon, M.D. (Site 754)

The site screened 13 subjects and enrolled 10 subjects. A record review was done for all 13 subjects. The inspection included review of all subject records including eCRFs, electronic medical histories including the radiology scans, and study specific hard copy folders containing inclusion/exclusion records, randomization confirmations, informed consent documentation, adverse and serious adverse events (SAE) documentation, correspondence, laboratory reports, and target lesion measurements obtained from the radiology scans. The source data was compared to the data listings submitted to the application.

The inspection revealed no significant deficiencies. The primary efficacy endpoint data were verifiable with the source records maintained at the site. There was no evidence of under-reporting of AEs.

4. (b) (4)

This inspection was issued to review the conduct of one clinical study (I3Y-MC-JPBM), performed in support of NDA 208855. The inspection focused primarily on assessing the accuracy of the tumor response and disease progression source records as it pertains to the contractual obligations of the CRO. Assessment of (b) (4) conduct of the Charter-Specified CRO responsibilities included training, education, and qualifications of radiologists, correspondence with clinical sites/sponsor, quality assurance, data collection and management and IRC Image Read Charter and adherence.

As of the data cut-off date, January 31, 2017, for analysis, (b) (4) had assessed one or more tumor response timepoints for 476 study subjects; a total of 2655 timepoints. Subject source documents and records generated by the CRO for 26 randomly selected subjects from 25 clinical sites were compared to the data listings submitted to the application. No discrepancies were noted.

There was no evidence of CRO non-compliance with the Charter.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Central Doc. Rm. NDA #208855
DOP1/Division Director (Acting)/Julia Beaver
DOP1/Clinical Team Leader/Laleh Amiri-Kordestani
DOP1/Project Manager/Janice Kim
DOP1/Medical Officer/Lynn Howie
OSI/Office Director (Acting)/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Susan D. Thompson
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/s/

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12/27/2017

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