CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208716Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
<table>
<thead>
<tr>
<th>Application Type</th>
<th>NDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application Number</td>
<td>208716</td>
</tr>
<tr>
<td>PDUFA Goal Date</td>
<td>January 5, 2018</td>
</tr>
<tr>
<td>OSE RCM #</td>
<td>2017-946</td>
</tr>
<tr>
<td></td>
<td>2017-950</td>
</tr>
<tr>
<td>Reviewer Name(s)</td>
<td>Ingrid N. Chapman, Pharm.D.</td>
</tr>
<tr>
<td>Team Leader</td>
<td>Elizabeth Everhart, MSN, ACNP</td>
</tr>
<tr>
<td>Division Director</td>
<td>Cynthia LaCivita, Pharm.D.</td>
</tr>
<tr>
<td>Review Completion Date</td>
<td>August 25, 2017</td>
</tr>
<tr>
<td>Subject</td>
<td>Evaluation of Need for a REMS</td>
</tr>
<tr>
<td>Established Name</td>
<td>Abemaciclib</td>
</tr>
<tr>
<td>Trade Name</td>
<td>Verzenio</td>
</tr>
<tr>
<td>Name of Applicant</td>
<td>Eli Lilly and Co.</td>
</tr>
<tr>
<td>Therapeutic Class</td>
<td>Cyclin Dependent Kinase 4 and 6 (CDK 4/6) Inhibitor</td>
</tr>
<tr>
<td>Formulation(s)</td>
<td>Tablets for oral use – 50 mg, 100 mg, 150 mg and 200 mg</td>
</tr>
<tr>
<td>Dosing Regimen</td>
<td>150 mg by mouth twice daily in combination with fulvestrant</td>
</tr>
<tr>
<td></td>
<td>200 mg by mouth twice daily as monotherapy</td>
</tr>
</tbody>
</table>
# Table of Contents

EXECUTIVE SUMMARY ......................................................................................................................................................... 3  

1  Introduction ..................................................................................................................................................................... 3  

2  Background ...................................................................................................................................................................... 3  
   2.1  Product Information ........................................................................................................................................... 3  
   2.2  Regulatory History............................................................................................................................................... 4  

3  Therapeutic Context and Treatment Options .................................................................................................... 4  
   3.1  Description of the Medical Condition .......................................................................................................... 4  
   3.2  Description of Current Treatment Options ............................................................................................... 4  

4  Benefit Assessment....................................................................................................................................................... 6  

5  Risk Assessment & Safe-Use Conditions ..............................................................................................................  6  
   5.1  Diarrhea ................................................................................................................................................................... 6  
   5.2  Neutropenia............................................................................................................................................................ 6  
   5.3  Hepatobiliary toxicity ......................................................................................................................................... 6  
   5.4  Embryo-Fetal toxicity ......................................................................................................................................... 7  
   5.5  Deaths....................................................................................................................................................................... 7  

6  Expected Postmarket Use........................................................................................................................................... 7  

7  Risk Management Activities Proposed by the Applicant ....................................................................................... 7  

8  Discussion of Need for a REMS................................................................................................................................. 8  

9  Conclusion & Recommendations............................................................................................................................. 8  

10  Appendices ................................................................................................................................................................ ....... 8  
   10.1  References............................................................................................................................................................... 8  
   10.2  Table 1: Summary of Treatment Options for Advanced and Metastatic Breast Cancer ....... 9  

Reference ID: 4144672
EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Verzenio (abemaciclib) is necessary to ensure the benefits outweigh its risks. Eli Lilly and Co. submitted a New Drug Application (NDA) 208716 for abemaciclib with the proposed indications: in combination with fulvestrant for the treatment of women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer with disease progression following endocrine therapy and as monotherapy for the treatment of patients with HR+, HER2- advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting. The risks associated with abemaciclib include diarrhea, neutropenia, embryo-fetal toxicity, increased blood creatinine, infections and thromboembolic events. The applicant did not submit a proposed REMS or risk management plan with this application.

The risks of abemaciclib are well known in oncology practice. If approved, the labeling will communicate the risks of abemaciclib with Warning and Precautions specifically highlighting the risks of diarrhea, neutropenia, and embryo-fetal toxicity. DRISK and the Division of Oncology Products (DOP-1) agree that a REMS is not needed to ensure the benefits of abemaciclib outweigh its risks.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Verzenio (abemaciclib) is necessary to ensure the benefits outweigh its risks. Eli Lilly and Co. submitted a New Drug Application (NDA) 208716 for abemaciclib with the proposed indications: in combination with fulvestrant for the treatment of women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer with disease progression following endocrine therapy and as monotherapy for the treatment of patients with HR+, HER2- advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting. This application is under review in the Division of Oncology Products 1. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Verzenio (abemaciclib), a new molecular entity, is a cyclin dependent kinase 4 and 6 (CDK 4/6) inhibitor with the proposed indications: in combination with fulvestrant for the treatment of women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer with disease progression following endocrine therapy and as monotherapy for the treatment of patients with HR+, HER2- advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.
Abemaciclib, if approved, will be the third drug in the pharmacologic class of CDK 4/6 inhibitors. The two CDK 4/6 inhibitors available in the U.S. market, Ibrance (palbociclib) and Kisqali (ribociclib), both were approved without a Boxed Warning or REMS.

Abemaciclib is proposed as 50 mg, 100 mg, 150 mg and 200 mg tablets for oral use. The recommended dose of abemaciclib is 150 mg by mouth twice daily in combination with fulvestrant or 200 mg by mouth twice daily as monotherapy. Treatment is continued until disease progression or unacceptable toxicity occurs. Abemaciclib was granted both breakthrough therapy designation and fast track designation and is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY
The following is a summary of the regulatory history for NDA 208716 relevant to this review:

- 09/15/2019: IND 106100 submission received for Verzenio
- 10/05/2015: Breakthrough Therapy designation granted
- 11/12/2015: Fast Track designation granted
- 05/05/2017: NDA 208716 submission received for Verzenio
- 06/28/2017: Priority Review designation granted
- 08/03/2017: Midcycle telecommunication with the applicant; the FDA stated there were no safety issues that require a REMS for abemaciclib

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION
In women, breast cancer is the most common cancer in the United States and the second leading cause of cancer death. Breast cancer is also the primary cause of death in women ages 45 to 55. In 2017, it is estimated that there will be 252,710 new cases of invasive (non-localized) female breast cancer. Approximately 40,610 people will die of this disease. The 5-year survival rate for distant (metastatic) breast cancer is 26.9% compared to 98.9% in those with localized disease.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS
Treatment of advanced or metastatic breast cancer is dependent upon many factors including the breast cancer stage, menopausal status, hormone receptor (estrogen and progesterone) presence, HER2 presence, and prior drug therapy. Nonpharmacologic treatment consists of breast-conserving surgery or

---

b Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.

c Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.

d Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.
mastectomy and radiation. For postmenopausal women with HR+, HER2- breast cancer, the mainstay of pharmacologic treatment is endocrine therapy with letrozole, anastrozole, exemestane and fulvestrant. Chemotherapy has significant toxicities and is reserved for patients with early life-threatening invasive disease in which time to treatment response is critical. See Table 1 in the appendix for more details.

Despite the availability of these medications, the prognoses in advanced breast cancer patients remain poor. Patients will eventually develop resistance to these medications, resulting in progression of disease. CDK 4/6 inhibitors are a relatively new pharmacologic class used for advanced and metastatic breast cancer. Progression-free survival is improved when CDK 4/6 inhibitors are combined with endocrine therapy compared to endocrine therapy alone.

4 Benefit Assessment

The efficacy and safety of abemaciclib for the treatment of HR+, HER2- advanced or metastatic breast cancer was demonstrated in two pivotal studies, JPBN (MONARCH 1) and JPBL (MONARCH 2). Both studies enrolled patients with HR+, HER2- metastatic breast cancer. MONARCH 1 was a multicenter, single-arm open-label Phase 2 study in 132 patients whose disease progressed after endocrine therapy and who received 1 or 2 prior chemotherapy regimens in the metastatic setting. The primary endpoint of MONARCH 1 was objective response rate (ORR) as defined by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1). The dosing regimen was abemaciclib 200 mg by mouth twice daily. Results showed an ORR of 19.7% and a secondary endpoint of median progression free survival (PFS) of 6 months.

MONARCH 2 was a global, double-blind, placebo-controlled phase 3 study in 669 patients who were endocrine therapy resistant. Endocrine therapy resistant was categorized as either relapsed on neoadjuvant therapy, relapsed within one year of adjuvant endocrine therapy, or progressed on first line endocrine therapy. The primary endpoint of MONARCH 2 was PFS. The dosing regimen for the treatment group (n = 441) in MONARCH 2 was initially abemaciclib 200 mg by mouth twice daily with fulvestrant 500 mg IM administered on days 1 and 15 of cycle 1 then on day 1 of cycle 2 and subsequent cycles (28-day cycles). The MONARCH 2 protocol was amended to reduce abemaciclib to 150 mg by mouth twice daily after an early trial level safety review. The protocol amendment was primarily due to the tolerability of abemaciclib and the adverse events, diarrhea and neutropenia. The placebo group (n = 223) received placebo plus fulvestrant at the same dose and frequency as the treatment group. Results showed a median PFS of 16.44 months compared to 9.27 months in the placebo group which was statistically significant. The ORR for Intent-To-Treat (ITT) was 35.2% in the treatment group versus 16.1% in the placebo group. For measurable disease, the ORR was 48.1% versus 21.3% in the treatment group vs placebo group, respectively.

The clinical team recommended regular approval of abemaciclib based on the efficacy and safety data provided by the applicant for the proposed indications: in combination with fulvestrant for the

---

*Section 505-1 (a) of the FD&C Act: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

Reference ID: 4144672
treatment of women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer with disease progression following endocrine therapy and as monotherapy for the treatment of patients with HR+, HER2- advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.\(^5\)

5 Risk Assessment & Safe-Use Conditions

The safety profile of abemaciclib for the proposed indications is based on safety data from the Phase 3 MONARCH 2 study and the Phase 2 MONARCH 1 study.\(^6\) A total of 573 patients were exposed to abemaciclib in these two trials. The serious adverse reactions (referred to as risks) determined to be associated with abemaciclib are diarrhea, neutropenia, hepatobiliary toxicity, embryo-fetal toxicity, increased blood creatinine, infections, and thromboembolic events.\(^f\) The Warnings and Precautions section of the proposed label includes the risks of diarrhea, neutropenia, and embryo-fetal toxicity. The pooled data for these risks and the deaths that occurred are discussed in the sections below.

5.1 DIARRHEA

Diarrhea occurred in 500/573 (87.3%) of patients with 85/573 (14.8%) experiencing Grade 3. Abemaciclib was discontinued by 14 patients and 113 patients required dose reductions due to diarrhea. The draft abemaciclib label includes diarrhea in the Warning and Precautions section with a recommendation to initiate antidiarrheal therapy at the first sign of loose stools.

5.2 NEUTROPENIA

Neutropenia occurred in 252/573 (44%) of patients with 129/573 (22.5%) experiencing Grade 3 and 20/573 (3.5%) experiencing Grade 4. Abemaciclib was discontinued by 7 patients and approximately 57 patients required dose reductions due to neutropenia. Neutropenia is addressed in the Warnings and Precautions section of the proposed labeling for abemaciclib with the recommendation to monitor complete blood counts at regular intervals.

5.3 HEPATOBILIARY TOXICITY

Liver function tests (LFTs), aspartate aminotransferase (AST) and alanine aminotransferase (ALT), increased in patients receiving abemaciclib in the MONARCH 2 study. Elevations in AST and ALT occurred in 54/573 (9.4%) and 59/573 (10.3%) respectively. Grade 3 elevations in AST occurred in 10/573 (1.7%) patients. Grade 3 elevations in ALT were reported in 17/573 (3%) patients and one patient had a Grade 4 increase in ALT. Six patients discontinued abemaciclib due to hepatic failure and

\(^{f}\) Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
5.4 **EMBRYO-FETAL TOXICITY**
Based on pre-clinical data, abemaciclib can cause fetal harm. In the proposed labeling, under Warnings and Precautions, patients are advised to use effective contraception while receiving treatment and at least 3 weeks after the last dose.

5.5 **DEATHS**
Overall, 23/573 (4%) patients died during treatment or within 30 days of discontinuation of abemaciclib in MONARCH 1 and MONARCH 2. Of the 9 deaths that occurred in MONARCH 1, 7 were due to study disease and 2 were attributed to adverse events (sepsis and pneumonitis). The death due to pneumonitis was categorized as an adverse event related to study drug. Of the 14 deaths in MONARCH 2, 5 were due to study disease and 9 were attributed to adverse events. The most common adverse event resulting in death was sepsis (n=3). Embolism, hepatic failure, hepatic function abnormal, lung infection, multiple organ dysfunction syndrome and pneumonitis resulted in an adverse event related death in one patient each. The cause of death considered related to study treatment was: 6 patients by the investigator, 3 patients by the applicant, and 2 patients by both the investigator and applicant.7

6 **Expected Postmarket Use**
Abemaciclib will be primarily prescribed in the outpatient setting by oncologists who are likely to be familiar with the management of adverse reactions associated with CDK 4/6 inhibitors. The draft prescribing information currently addresses the associated serious risks and management of diarrhea, neutropenia, maternal-fetal toxicity, increased blood creatinine, infection and thromboembolic events.

7 **Risk Management Activities Proposed by the Applicant**
The applicant did not propose any risk management activities beyond labeling and routine pharmacovigilance for abemaciclib.

8 **Discussion of Need for a REMS**
The Clinical Team recommends approval of abemaciclib on the basis of the efficacy and safety information currently available. Advanced and metastatic breast cancer is a serious disease with over 250,000 women likely to be diagnosed in 2017. Approximately 74% of those diagnosed will have the HR+, HER2- breast cancer subtype.8 The standard treatment of HR+, HER2- breast cancer with endocrine therapy is effective in providing PFS but its use is limited due to intrinsic and acquired resistance. Abemaciclib targets CDK 4/6 which may be involved in mechanism of endocrine resistance. Therefore, abemaciclib is beneficial in improving PFS and possibly reducing the risk of endocrine resistance.
The serious risks associated with abemaciclib are diarrhea, neutropenia, hepatobiliary toxicity, maternal-fetal toxicity, increased blood creatinine, infections and thromboembolic events. Oncology healthcare providers who prescribe abemaciclib should be familiar with managing the risks with abemaciclib as they are well known in this specialty. The two marketed CDK 4/6 inhibitors share similar risk-benefit profiles and were approved without a REMS or boxed warning. The labeling will be used to communicate these risks. DRISK recommends that, should abemaciclib be approved, a REMS is not necessary to ensure its benefits outweigh its risks.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable and therefore, a REMS is not necessary for abemaciclib to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 REFERENCES

### Table 19: Summary of Treatment Options for Advanced and Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Product Trade Name (Generic) Year Approved</th>
<th>Year Approved</th>
<th>Important Safety and Tolerability Issues</th>
<th>Risk Management Approaches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soltamox (Tamoxifen) (^a)SERM</td>
<td>1977</td>
<td>Uterine malignancies Stroke Pulmonary embolism</td>
<td>Labeling – Boxed Warning</td>
</tr>
<tr>
<td>Arimidex (Anastrozole) (^b)AI, nonsteroidal</td>
<td>1995</td>
<td>Ischemic cardiovascular events, decreased bone mineral density (BMD) and elevated cholesterol</td>
<td>Labeling – Warning and Precautions</td>
</tr>
<tr>
<td>Femara (Letrozole) AI, nonsteroidal</td>
<td>1997</td>
<td>Decreased BMD Elevated cholesterol</td>
<td>Labeling – Warning and Precautions</td>
</tr>
<tr>
<td>Aromasin (Exemestane) AI, steroidal</td>
<td>1999</td>
<td>Decreased BMD Lymphopenia Elevated liver enzymes Drug-drug interactions</td>
<td>Labeling – Warning and Precautions</td>
</tr>
<tr>
<td>Faslodex (Fulvestrant) Estrogen receptor antagonist</td>
<td>2002</td>
<td>Bleeding disorders Injection-site related events Benzyl alcohol</td>
<td>Labeling – Warning and Precautions</td>
</tr>
<tr>
<td>Afinitor (Everolimus) mTOR kinase inhibitor</td>
<td>2009</td>
<td>Immunosuppression Pulmonary toxicity Infections Hepatic impairment Renal effects</td>
<td>Labeling – Warning and Precautions</td>
</tr>
<tr>
<td>Ibrance (Palbociclib) CDK 4/6 inhibitor</td>
<td>2015</td>
<td>Bone marrow suppression Infection GI toxicity Drug-drug interactions (DDI)</td>
<td>Labeling – Warning and Precautions</td>
</tr>
<tr>
<td>Kisqali (Ribociclib) CDK 4/6 inhibitor</td>
<td>2017</td>
<td>Bone marrow suppression QT prolongation Hepatobiliary toxicity DDI</td>
<td>Labeling – Warning and Precautions</td>
</tr>
<tr>
<td>Kisqali Femara (Ribociclib &amp; Letrozole) Co-packaged Product</td>
<td>2017</td>
<td>As above for each individual product</td>
<td>As above for each individual product</td>
</tr>
</tbody>
</table>

\(^a\)SERM = Selective estrogen receptor modulator  
\(^b\)AI = aromatase inhibitor
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

INGRID N CHAPMAN
08/25/2017

CYNTHIA L LACIVITA
08/25/2017
Concur