CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	208855
PDUFA Goal Date	April 15, 2018
OSE RCM #	2017-1682 2017-1821
Reviewer Name(s)	Ingrid N. Chapman, Pharm.D.
Team Leader	Elizabeth Everhart, MSN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	February 20, 2018
Subject	Evaluation of Need for a REMS
Established Name	Abemaciclib
Trade Name	Verzenio
Name of Applicant	Eli Lilly and Co.
Therapeutic Class	Cyclin Dependent Kinase 4 and 6 (CDK 4/6) Inhibitor
Formulation(s)	Tablets for oral use – 50 mg, 100 mg, 150 mg and 200 mg
Dosing Regimen	150 mg by mouth twice daily in combination with fulvestrant or an aromatase inhibitor 200 mg by mouth twice daily as monotherapy

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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) 208855 for abemaciclib with the following proposed indications.

Verzenio (b) (4) is a kinase inhibitor indicated (b) (4)

- in combination with an aromatase inhibitor as initial endocrine-based therapy;
- in combination with fulvestrant (b) (4) following endocrine therapy;
- as (b) (4) with disease progression following endocrine therapy and (b) (4) prior chemotherapy regimens in the metastatic setting.

Verzenio was originally approved under NDA 208716 on September 28, 2017 with the following indications; Verzenio is indicated: in combination with fulvestrant for the treatment of women with HR-positive, 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. Labeling negotiations with NDA 208716 were ongoing when NDA 208855 was submitted accounting for the difference in the proposed indication for NDA 208855 and the approved indication for NDA 208716.

The risks associated with abemaciclib include diarrhea, neutropenia, hepatotoxicity, 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 and the management of those risks are similar to the approved kinase inhibitors used in the treatment of breast cancer, palbociclib and ribociclib. If approved, the labeling will continue to communicate the risks of abemaciclib with Warning and Precautions specifically highlighting the risks of diarrhea, neutropenia, hepatotoxicity, venous thromboembolism 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 Lily and Co. submitted a New Drug Application (NDA) 208855 for abemaciclib with the following proposed indications; Verzenio (b) (4) is a kinase inhibitor indicated (b) (4)

- in combination with an aromatase inhibitor as initial endocrine-based therapy;
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2 Background

2.1 Product Information

Verzenio™ (abemaciclib), a new molecular entity,[a] is a cyclin dependent kinase 4 and 6 (CDK 4/6) inhibitor with the following proposed indications. Verzenio™ (b) (4) is a kinase inhibitor indicated (b) (4) : in combination with an aromatase inhibitor as initial endocrine-based therapy; in combination with fulvestrant (b) (4) following endocrine therapy; (b) (4) with disease progression following endocrine therapy and (b) (4) prior chemotherapy regimens in the metastatic setting. The two CDK 4/6 inhibitors available in the U.S. market prior to abemaciclib, Ibrance (palbociclib) and Kisqali (ribociclib), were both approved without a Boxed Warning or REMS. Abemaciclib, the third CDK 4/6 inhibitor, was initially approved under NDA 208716 on September 28, 2017 without a REMS.

Abemaciclib is available 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 endocrine therapy or 200 mg by mouth twice daily as monotherapy. Treatment is continued until disease progression or unacceptable toxicity occurs.[b] Abemaciclib was granted both breakthrough therapy and fast track designation.

2.2 Regulatory History

The following is a summary of the regulatory history for abemaciclib relevant to this review:

- 09/15/2009: IND 106100 submission received for abemaciclib
- 10/05/2015: Breakthrough Therapy designation granted
- 11/12/2015: Fast Track designation granted
- 05/05/2017: NDA 208716 submission received for abemaciclib

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

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

- 06/28/2017: Priority Review designation granted
- 08/03/2017: Midcycle telecommunication with the applicant for NDA 208716; the FDA stated there were no safety issues that require a REMS for abemaciclib
- 08/15/2017: NDA 208855 submission received for abemaciclib
- 09/28/2017: NDA 208716 approved
- 11/14/2017: Midcycle telecommunication with the applicant for NDA 208855; 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.[c] Breast cancer is also the primary cause of death in women ages 45 to 55.[2] In 2017, it is estimated that there will be 252,710 new cases of invasive (non-localized) female breast cancer.[d] 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]

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 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.[4] 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.

[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.*

4 Benefit Assessment[e]

The efficacy and safety of abemaciclib for the treatment of HR+, HER2- advanced or metastatic breast cancer was demonstrated in three pivotal studies, JPBN (MONARCH 1), JPBL (MONARCH 2) and JPBM (MONARCH 3).[5,6] A summary of the MONARCH 3 and the endocrine-naive cohort of MONARCH 2 studies are provided .

MONARCH 3 was a global, double-blind, placebo-controlled phase 3 study in 493 patients (postmenopausal women) with HR+, HER2- advanced or metastatic breast cancer with no prior treatment for advanced disease. The primary endpoint was investigator-determined median progression-free survival (PFS). The dosing regimen for the treatment group (n = 328) was abemaciclib 150 mg by mouth twice daily plus an aromatase inhibitor (letrozole or anastrazole). Letrozole was dosed at 2.5 mg by mouth daily and anastrazole was dosed at 1 mg by mouth daily. The placebo group (n = 165) received placebo plus an aromatase inhibitor at the same dose and frequency as the treatment group. Results showed a median PFS of 28.2 months in the treatment group compared to 14.8 months in the placebo group which was statistically significant. The overall response rate (ORR; complete response + partial response) for the treatment group was 49.7% compared to 37% in the placebo group.

MONARCH 2 was a global, double-blind, placebo-controlled phase 3 study in 669 patients that included an endocrine-naïve cohort of 43 patients. The endocrine-naïve cohort data was removed from the intent-to-treat population and analyzed separately. The dosing regimen for the endocrine-naive treatment group (n = 27) varied based on when the patient entered the study. Twenty-one patients initially received abemaciclib 200 mg by mouth every 12 hours and 6 patients received the amended dose of abemaciclib 150 mg by mouth every 12 hours. Fulvestrant was dosed at 500 mg intramuscularly administered on days 1 and 15 of cycle 1 then on day 1 of cycle 2 and subsequent cycles (28-day cycles). The endocrine-naïve placebo group (n = 16) received placebo plus fulvestrant at the same dose and frequency as the treatment group. Median PFS was not reached in the treatment group while the placebo group had a median PFS of 23.1 months. Eighteen patients experienced PFS events (disease progression or death) with 9 events in the treatment group (32.1%) and 9 in the placebo group (56.3%). The hazard ratio was 0.454 (95% confidence interval: 0.179, 1.154) which was not statistically significant.[7]

The clinical team (clinical reviewer, cross-discipline team leader and statistical reviewer) recommends regular approval of abemaciclib based on the efficacy and safety data provided by the applicant for the following additional indication: in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor HR+, HER2- advanced or metastatic breast cancer). The following revised indication proposed by the applicant was not recommended for approval: in combination with fulvestrant (b) (4) for the treatment of women with hormone receptor (HR)-positive, human epidermal

[e] 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.*

growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.[8]

5 Risk Assessment & Safe-Use Conditions

The safety profile of abemaciclib was initially established by the safety data from the Phase 3 MONARCH 2 study and the Phase 2 MONARCH 1 study.[9] With the addition of the Phase 3 MONARCH 3 data, a total of 1066 patients were exposed to abemaciclib in these three trials. The serious adverse events associated with abemaciclib, diarrhea, neutropenia, hepatotoxicity, venous thromboembolism and embryo-fetal toxicity are communicated through Warnings and Precautions in the label.[f] No new serious events were determined from the MONARCH 3 study. The deaths that occurred are discussed in the section below.

5.1 DEATHS

In MONARCH 3, 13 (4%) patients died during treatment or within 30 days of abemaciclib discontinuation. Of the 13 deaths, 3 were due to disease progression and 10 were due to adverse events. Of the 10 deaths deemed due to adverse events, 5 were further categorized as adverse events related to study drug (cerebral ischemia, cerebrovascular accident, lung infection, pneumonitis and respiratory failure).[10] The most common adverse event resulting in death was lung infection (n = 3) followed by embolism (n = 2) and pneumonitis (n = 2). In the endocrine-naïve cohort of MONARCH 2, 1 (3.7%) patient died due to an adverse event of respiratory failure.[11]

6 Expected Postmarket Use

Abemaciclib will be primarily prescribed in the outpatient setting and the likely prescribers will be oncologists. The risks are similar to the approved kinase inhibitors palbociclib and ribociclib) used in the treatment of breast cancer and prescribers are likely to be familiar with the management of adverse reactions associated with CDK 4/6 inhibitors. The prescribing information currently addresses the associated serious risks and management of diarrhea, neutropenia, hepatotoxicity, venous thromboembolism and embryo-fetal toxicity.

[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.

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

DOP-1 including the clinical, clinical pharmacology, statistical, and toxicology reviewer, recommends approval of abemaciclib based on 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.[12] 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 the 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 include diarrhea, neutropenia, hepatotoxicity, embryo-fetal toxicity, increased blood creatinine, infections and thromboembolic events. They are currently communicated through Warnings and Precautions in labeling. Oncology healthcare providers are the likely prescribers of abemaciclib and should be familiar with managing these risks. Since abemaciclib was approved under NDA 208716, no new safety signals have occurred. DRISK recommends that, should NDA 208855 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

1. Eli Lilly and Co. Verzenio (abemaciclib), Prescribing Information. September 28, 2017.
2. Taghian A, El-Ghamry MN, Merajver SD. Overview of the treatment of newly diagnosed, non-metastatic breast cancer. *UpToDate.* 2016. Accessed June 15, 2017.
3. Howlader N, Noone A, Krapcho M, et al. Cancer Stat Facts: Female Breast Cancer. 2017; https://seer.cancer.gov/statfacts/html/breast.html. Accessed June 15, 2017.
4. Denduluri N, Somerfield MR, Eisen A, et al. Selection of Optimal Adjuvant Chemotherapy Regimens for Human Epidermal Growth Factor Receptor 2 (HER2) –Negative and Adjuvant Targeted Therapy for HER2-Positive Breast Cancers: An American Society of Clinical Oncology Guideline Adaptation of the Cancer Care Ontario Clinical Practice Guideline. *Journal of Clinical Oncology.* 2016;34(20):2416-2427.

5. Eli Lilly and Co. Verzenio (abemaciclib), Applicant Orientation Meeting for NDA 208716. June 16, 2017.
6. Eli Lilly and Co. Verzenio (abemaciclib), Application Orientation Meeting for NDA 208855. September 28, 2017.
7. Eli Lilly and Co. Verzenio (abemaciclib), Module 2.5 - Clinical Overview for NDA 208855. July 24, 2017.
8. Howie L. Division of Oncology Products 1. Verzenio (abemaciclib) Mid-Cycle Meeting, Clinical Reviewer Slides (NDA 208855). November 9, 2017.
9. Eli Lilly and Co. Verzenio (abemaciclib), Module 2.5 - Clinical Overview. May 5, 2017.
10. Eli Lilly and Co. Verzenio (abemaciclib), 90-Day Update of Safety Information for NDA 208855 November 8, 2017.
11. Eli Lilly and Co. Verzenio (abemaciclib), Module 2.7.4 - Summary of Clinical Safety for NDA 208855.
. July 17, 2017.
12. American Cancer Society. Breast Cancer Facts & Figures 2015-2016. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2015-2016.pdf.
13. Drugs@FDA: FDA Approved Drug Products. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed August 1, 2017.

10.1 TABLE 1[13]: SUMMARY OF TREATMENT OPTIONS FOR ADVANCED AND METASTATIC BREAST CANCER

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

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