CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
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	218881
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Reviewer Name(s)	Ingrid N. Chapman, PharmD, BCPS, DRM
Team Leader(s)	Naomi Boston, PharmD, DRM
Acting Division Director	Laura Zendel, PharmD, DRM
Review Completion Date	September 25, 2025
Subject	Evaluation of Need for a REMS
[Established/Proper] Name	Imlunestrant
Trade Name	Inluriyo
Name of Applicant	Eli Lilly and Co.
Therapeutic Class	Estrogen receptor antagonist
Dosage Form	200 mg tablets for oral administration
Dosing Regimen	400 mg by mouth once daily (without food)

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Inluriyo (imlunestrant) is necessary to ensure the benefits outweigh its risks.

Eli Lilly and Co. submitted a New Drug Application (NDA) 218881 for imlunestrant with the proposed indication: for the treatment of adults with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer, previously treated with an endocrine-based regimen. During the course of the review, the indication was revised to the following:

> For the treatment of adults with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, estrogen receptor-1 (ESR1)-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

This application was reviewed by the Division of Oncology 1 (DO1). The efficacy of imlunestrant was demonstrated in the EMBER-3 trial. EMBER-3 demonstrated a statistically significant and clinically meaningful improvement in PFS by investigator assessment in the *ESR1*m population. For the imlunestrant arm, median progression free survival (PFS) was 5.5 months versus 3.8 months in the treatment of physician's choice (TPC) arm (HR 0.62, 95% CI: 0.46-0.82; p-value 0.0008). The review team concluded that this demonstrates substantial evidence of effectiveness.

The serious risk associated with imlunestrant includes embryo-fetal toxicity. The Applicant did not submit a proposed REMS or risk management plan with this application.

DRM has determined that a REMS is not needed to ensure the benefits of imlunestrant outweigh its risks. FDA expects the labeling to be sufficient to communicate the risk of embryo-fetal toxicity. FDA also expects the likely prescribers of imlunestrant (oncologists) to be familiar with managing embryo-fetal toxicity risk because other products they prescribe have this similar risk.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Inluriyo (imlunestrant) is necessary to ensure the benefits outweigh its risks. Eli Lilly and Co. submitted a New Drug Application (NDA) 218881 for imlunestrant with the proposed indication: for the treatment of adults with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer, previously treated with an endocrine-based regimen.[1] This application was reviewed by the Division of Oncology 1 (DO1). The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Inluriyo (imlunestrant), a new molecular entity (NME),[a] is an estrogen receptor antagonist and selective estrogen receptor degrader (SERD) proposed for the treatment of adults with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer, previously treated with an endocrine-based regimen.[1]

Imlunestrant is proposed as 200 mg tablets for oral administration. The recommended dosage is 400 mg by mouth once daily without food. Treatment with imlunestrant is continued indefinitely or until unacceptable toxicity occurs.[1,b] Imlunestrant is not currently approved in any other jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 218881 relevant to this review:

- **10/31/2024**: NDA 218881 submission for the treatment of adults with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer, previously treated with an endocrine-based regimen.
- **05/06/2025**: A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for imlunestrant.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

In women, breast cancer is the most common cancer and the fourth leading cause of cancer death in the United States.[c] In 2025, it is estimated that there will be 316,950 new cases of female breast cancer and 42,170 deaths.[2] The breast cancer subtype, HR-positive/HER2-negative (HR+/HER2-), is the most common (68% of all cases) molecular subtype with an age-adjusted rate of 87.2 new cases per 100,000 women, based on 2016–2020 cases.[2,3,d] The 5-year survival rate for HR+/HER2- is 94.8% (localized: 100%; regional: 90.3%; and distant/metastatic: 34%). Acquired ESR1-mutations are estimated to range anywhere from 10-50% in the advanced and metastatic setting after prior exposure to prior endocrine therapy, especially aromatase inhibitors.[4] ER-positive, HER2-negative (ESR1)-mutated advanced or metastatic breast cancer is a serious and life-threatening condition.

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,

[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.*
[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.*

HER2 presence, and prior drug therapy. Nonpharmacologic treatment consists of breast-conserving surgery or mastectomy and radiation. To aid in treatment selection, the American Society of Clinical Oncology (ASCO) Guideline Rapid Recommendation Update recommends routine testing for the emergence of estrogen receptor 1 (*ESR1)* gene mutations at recurrence or progression on endocrine therapy (with or without a cyclin-dependent kinase 4/6 inhibitor with ER-positive, HER2- metastatic breast cancer).[5]

Because endocrine therapy alone or in combination with targeted agents has comparable outcomes and less toxicity, it is the preferred regimen over chemotherapy. Chemotherapy is reserved for patients with early life-threatening invasive disease in which time to treatment response is critical.[6]

FDA-approved drugs for the treatment of HR+/HER2- metastatic breast cancer include:

- Aromatase inhibitors (AI): letrozole, anastrozole, and exemestane
- Cyclin-dependent kinase (CDK) 4/6 inhibitors: palbociclib, ribociclib, and abemaciclib
- mTOR kinase inhibitor: everolimus
- Selective estrogen receptor modulator (SERM): tamoxifen
- Poly (ADP-ribose) polymerase (PARP) inhibitors: talazoparib and olaparib; PARP inhibitors are reserved for those with germline *BRCA 1/2* mutation.
- Selective estrogen receptor degraders (SERDs): fulvestrant and elacestrant

The preferred first-line treatment for patients with ER-positive, HER2-negative advanced or metastatic breast cancer in the U.S. is a CDK4/6 inhibitor in combination with endocrine therapy (an AI or fulvestrant).[4] Acquired resistance to endocrine therapy, particularly AIs, can occur due to activating missense mutations and in-frame deletions in the ligand-binding domain (LBD) of *ESR1*. It is estimated that approximately 10-50% of patients exposed to an AI for treatment of metastatic breast cancer will acquire tumor *ESR1* mutation(s).[4] Additionally, AIs may be less effective in patients with ESR1-mutated breast cancer because this type of cancer is likely resistant to estrogen depletion.[7]

Elacestrant was FDA-approved for *ESR1*-mutated breast cancer in January 2023. Specifically, elacestrant is indicated for the treatment of estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, ESR1-mutated advanced or metastatic breast cancer in postmenopausal patients or adult males with disease progression following at least 1 line of endocrine therapy.[7]

Advanced or metastatic breast cancer remains incurable. Treatment is palliative, with the aims of reducing cancer-related symptoms, delaying disease progression, and prolonging survival. [e] There remains an unmet need for additional therapies that may offer an additional option to improve clinical outcomes in all patients with ER-positive, HER2-negative advanced or metastatic breast cancer, including patients with *ESR1* mutations.[4] Refer to Table 10.1 in the appendix for a summarization of the treatment options currently available.

[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.*

4. Benefit Assessment

The efficacy and safety assessment for imlunestrant is primarily based on data from the EMBER-3 trial (NCT04975308). EMBER-3 was a randomized, open-label, active-controlled, multicenter trial that enrolled 874 adult patients with ER+, HER2- locally advanced or metastatic breast cancer, who were previously treated with an aromatase inhibitor either alone or in combination with a CDK4/6 inhibitor. Patients were excluded if they were eligible to receive a PARP inhibitor (n = 323 with *ESR1m* disease). Patients were required to have progressed:[8]

- Within 12 months of completing neoadjuvant or adjuvant aromatase inhibitor therapy with no systemic treatment for recurrent disease or
- Greater than 12 months after neoadjuvant or adjuvant endocrine therapy or de novo metastatic disease and had progressed on only one line of aromatase inhibitor therapy.

Patients were randomized 1:1:1 to imlunestrant 400 mg orally once daily; or treatment of physician's choice (TPC) [fulvestrant 500 mg IM on days 1, 15, 29, and once monthly thereafter (n=111) or exemestane 25 mg orally once daily (n=6)]; or an additional investigational combination regimen. Patients were treated until disease progression or unacceptable toxicity. The major efficacy outcome was investigator assessed progression-free survival (PFS) in the *ESR1m* population and the intent to treat (ITT) population (*ESR1m* and *ESR1m*-not detected). The other efficacy measures were overall survival (OS) in the *ESR1m* and ITT populations.[4]

Results showed there was a statistically significant difference in investigator-assessed PFS in the *ESR1*m population for imlunestrant compared to investigator's choice of endocrine therapy (fulvestrant or exemestane).[8] Median PFS was 5.5 months versus 3.8 months (HR 0.62, 95% CI: 0.46-0.82; p-value 0.0008). The PFS endpoint in the ITT population did not cross the prespecified significance alpha level and therefore was not statistically significant. The secondary OS endpoint in the *ESR1*m population was immature (31% maturity) and not statistically significant (HR 0.55, 95% CI: 0.35-0.86). OS could not be tested in the ITT population since PFS in the overall population failed to meet the prespecified threshold.[4]

The FDA review team concluded that for patients in the *ESR1*m population, the benefit-risk assessment for imlunestrant was favorable given the statistically significant improvement in PFS, which was robust to multiple sensitivity analyses and supported by a positive overall survival and hazard ratio trend (despite OS being immature).[4]

DO1 revised the proposed indication to accurately reflect the patient population enrolled in the EMBER-3 trial. Although there were no male patients in the *ESR1*m population, the FDA included male patients in the indication based on extrapolation from the data in female patients and the biologic rationale that there were no expected efficacy or safety differences between male and female patients with an *ESR1*m (FDA Guidance: Male Breast Cancer, 2020).

The indication for approval is:[4]

> Imlunestrant is indicated for the treatment of adults with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, estrogen receptor-1 (ESR1)-mutated advanced

or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

5. Risk Assessment & Safe-Use Conditions

The primary safety population for imlunestrant consists of all subjects in the randomized population who received imlunestrant at 400 mg by mouth once daily in the EMBER-3 trial (n = 327). The median duration of exposure for these subjects was 5.6 months (range: 0.2 to 28.6 months).[8]

The safety profile of imlunestrant was generally reflective of an endocrine therapy, with mostly Grade 1-2 adverse reactions.[4] Serious adverse reactions (SARs) occurred in 10% of subjects who received imlunestrant compared to 11% in subjects who received TPC. SARs that occurred in > 1% of patients receiving imlunestrant included pleural effusion (1.2%) and in TPC included fracture (1.5%).[8] Fatal adverse reactions occurred in 1.8% of patients who received imlunestrant, including cardiac arrest, acute myocardial infarction, right ventricular failure, hypovolemic shock, and upper gastrointestinal hemorrhage (each 0.3%).[8] The FDA generally agrees with the Applicant's position that the majority of deaths were due to study disease.[4]

Labeling[f] includes one SAR, embryo-fetal toxicity, in the Warnings and Precautions. Based on findings in animals and its mechanism of action, imlunestrant can cause fetal harm when administered to a pregnant woman. In an animal reproduction study, oral administration of imlunestrant to pregnant rats during the period of organogenesis led to embryo-fetal mortality and structural abnormalities at maternal exposures that were below the human exposure at the recommended dose based on area under the curve (AUC). No other new or serious risks were identified; no other safety signals were identified for this product.

The safe use conditions for imlunestrant and embryo-fetal toxicity include:[8]

- Pregnant women and females of reproductive potential should be advised of the potential risk to a fetus.
- Females of reproductive potential and male patients with female partners of reproductive potential should be advised to use effective contraception during treatment with imlunestrant and for one week after the last dose.

6. Expected Postmarket Use

Patients with ER+, HER2-, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy should have an established relationship with healthcare provider. The likely prescribers of imlunestrant are oncologists. If approved, imlunestrant will likely be dispensed from outpatient pharmacy settings and primarily be self-administered by the patient at home. Based on the anticipated medication use process, monitoring for embryo-fetal toxicity should be a collaborative effort between the prescriber and the patient or patient's caregiver. No concerning care gaps have been identified within the intended scope of practice. Labeling is sufficient to ensure the safe-

use conditions, described in Section 5, for mitigating the risk of imlunestrant in the expected postmarket setting.

7. Discussion of the Need for a REMS

Based on the efficacy and safety information currently available, FDA determined that a REMS is not necessary to ensure the benefits of imlunestrant outweigh the risks. Embryo-fetal toxicity, which is based on an animal reproduction study, is the risk listed in the Warnings and Precautions section of the proposed label. FDA expects the labeling to be sufficient to communicate this risk. FDA also expects the likely prescribers of imlunestrant (oncologists) to be familiar with managing embryo-fetal toxicity risk because other products they prescribe have this similar risk.

8. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for imlunestrant beyond routine pharmacovigilance and labeling. The Applicant states,[4] "Potential safety concerns beyond the risks conveyed in the proposed labeling are not expected. Routine pharmacovigilance practices will be used to monitor for unexpected events."

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for imlunestrant to ensure the benefits outweigh the risks. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendix

10.1. Table 1[9]: FDA-Approved Options for HR+/HER2- Metastatic Breast Cancer

Trade Name (Generic) & Drug Class	Year Approved	Important Safety and Tolerability Issues	Risk Management Approaches
tamoxifen [a]SERM	12/30/1977	Uterine malignancies Stroke Pulmonary embolism	Labeling – Boxed Warning
Arimidex (anastrozole) [b]AI, nonsteroidal	12/27/1995	Ischemic cardiovascular events, decreased bone mineral density (BMD) and elevated cholesterol	Labeling – Warning and Precautions
Femara (letrozole) AI, nonsteroidal	07/25/1997	Decreased BMD Elevated cholesterol	Labeling – Warning and Precautions
Aromasin (exemestane) AI, steroidal	10/21/1999	Decreased BMD Lymphopenia Elevated liver enzymes Drug-drug interactions	Labeling – Warning and Precautions
Faslodex (fulvestrant) Estrogen receptor antagonist	04/25/2002	Bleeding disorders Injection-site related events Benzyl alcohol	Labeling – Warning and Precautions
Afinitor (everolimus) mTOR kinase inhibitor	03/30/2009	Immunosuppression Pulmonary toxicity Infections Hepatic impairment Renal effects	Labeling – Warning and Precautions
Ibrance (palbociclib) CDK 4/6 inhibitor	02/13/2015	Bone marrow suppression Infection GI toxicity Drug-drug interactions (DDI)	Labeling – Warning and Precautions
Kisqali (ribociclib) CDK 4/6 inhibitor	03/13/2017	Bone marrow suppression QT prolongation Hepatobiliary toxicity DDI	Labeling – Warning and Precautions
Lynparza (olaparib) poly (ADP-ribose) polymerase inhibitor /PARP inhibitor	08/17/2017	Myelodysplastic Syndrome/Acute Myeloid Leukemia (AML) Pneumonitis Venous Thromboembolism Embryo-Fetal Toxicity	Labeling – Warning and Precautions
Verzenio (abemaciclib) CDK 4/6 inhibitor	09/28/2017	Diarrhea Neutropenia Interstitial Lung Disease or Pneumonitis Hepatoxicity Venous Thromboembolism Embryo-Fetal Toxicity	Labeling – Warning and Precautions
Talzenna (talazoparib) PARP inhibitor	10/16/2018	Myelodysplastic Syndrome/AML Myelosuppression Embryo-Fetal Toxicity	Labeling – Warning and Precautions
Orserdu (elacestrant) Estrogen receptor antagonist	01/27/2023	Dyslipidemia Embryo-Fetal Toxicity	Labeling – Warning and Precautions
Truqap (capivasertib) Kinase inhibitor	11/17/2023	Hyperglycemia Diarrhea Cutaneous Adverse Reactions Embryo-Fetal Toxicity	Labeling – Warning and Precautions

[a]SERM = Selective estrogen receptor modulator
[b]AI = aromatase inhibitor

11. References

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