CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217639Orig1s000

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	217639
PDUFA Goal Date	February 17, 2023
TTT #	2022-245
Reviewer Name(s)	Brad Moriyama, Pharm.D., BCCCP
Team Leader	Naomi Boston, Pharm.D
Associate Director for REMS Design and Evaluation:	Laura Zendel, Pharm.D., BCPS
Review Completion Date	January 25, 2023
Subject	Evaluation of Need for a REMS
Established Name	Elacestrant
Trade Name	Orserdu
Name of Applicant	Stemline Therapeutics, Inc.
Therapeutic Class	estrogen receptor antagonist
Formulation(s)	86 mg and 345 mg tablet
Dosing Regimen	345 mg orally once daily

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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) Orserdu (elacestrant) is necessary to ensure the benefits outweigh its risks. Stemline Therapeutics, Inc. submitted a New Drug Application (NDA) 217639 for elacestrant with the proposed indication for treatment of postmenopausal women and men, with (b) (4)-positive, HER2-negative advanced or metastatic breast cancer who have progressed following at least one line of endocrine therapy. The FDA approved indication will be for treatment of postmenopausal women or adult men, with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy. The serious risks associated with elacestrant include dyslipidemia and embryo-fetal toxicity. The applicant did not submit a proposed REMS or risk management plan.

DRM and Division of Oncology 1 (DO1) agree that a REMS is not necessary to ensure the benefits of elacestrant outweigh its risks. The efficacy of elacestrant was supported by the EMERALD study, in which in patients with *ESR1* mutations the elacestrant group had a median progression-free survival (PFS) of 3.8 months and the fulvestrant or an aromatase inhibitor group had a median PFS of 1.9 months, hazard ratio 0.55. The serious risks associated with elacestrant of dyslipidemia and embryo-fetal toxicity will be communicated in the warnings and precautions section of the label. The likely prescribers will be hematologists and oncologists who should have experience managing the serious adverse events reported with elacestrant.

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)[a] Orserdu (elacestrant) is necessary to ensure the benefits outweigh its risks. Stemline Therapeutics, Inc. submitted a New Drug Application (NDA) 217639 for elacestrant with the proposed indication for the treatment of postmenopausal women and men, with (b) (4)-positive, HER2-negative advanced or metastatic breast cancer who have progressed following at least one line of endocrine therapy.[1] The FDA approved indication will be for treatment of postmenopausal women or adult men, with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy. This application is under review in the Division of Oncology 1 (DO1). The applicant did not submit a proposed REMS or risk management plan.

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

2. Background

2.1. Product Information

Orserdu (elacestrant), a NME, is an estrogen receptor antagonist, proposed for treatment of postmenopausal women and men, with (b) (4)-positive, HER2-negative advanced or metastatic breast cancer who have progressed following at least one line of endocrine therapy. Elacestrant is proposed to be supplied as an 86 mg and 345 mg tablet. The proposed dosing regimen is elacestrant 345 mg orally once daily until disease progression or unacceptable toxicity occurs.[b] Elacestrant is not currently approved in any jurisdiction. Elacestrant has received fast track designation.

2.2. Regulatory History

The following is a summary of the regulatory history for elacestrant NDA 217639 relevant to this review:

- 10/17/2017: Fast track designation granted
- 06/17/2022: NDA 217639 submission for treatment of postmenopausal women and men, with (b) (4)-positive, HER2-negative advanced or metastatic breast cancer who have progressed following at least one line of endocrine therapy received
- 12/01/2022: A Post Late-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 elacestrant

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Breast cancer is a common cause of cancer in women in the United States.[2] The estimated number of new cases of breast cancer in the United States in women and in men is 287,850 and 2710, respectively.[3,c] Histopathological subtypes of breast cancer are defined by expression of the estrogen receptor (ER), progesterone receptor (PR), and/or human epidermal growth factor receptor 2 (HER2).[4] Approximately 70% of patients with breast cancer will have ER-positive, HER2-negative disease. Furthermore, the estimated number of women with metastatic breast cancer in the United States in

[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 (A): The estimated size of the population likely to use the drug involved.*

2017 was 154,794.[5] Metastatic breast cancer is currently not curable and the five year relative survival of distant breast cancer is 30%.[2,6,d]

3.2. Description of Current Treatment Options

The treatment of recurrent or stage IV breast cancer increases survival and quality of life.[2] Current guidelines from the National Comprehensive Cancer Network (NCCN) for Breast Cancer list an aromatase inhibitor + CDK4/6 inhibitor, fulvestrant + non-steroidal aromatase inhibitor, and fulvestrant + CDK4/6 inhibitor as first line therapy in the "Preferred Regimens" section for systemic therapy for ER - and/or PR-positive HER2-negative recurrent unresectable or stage IV disease.

The NCCN guideline state that HR-positive breast cancer patients with disease progression may benefit from sequential use of endocrine therapies. In the "Other Recommended Regimens" section, the NCCN guidelines recommend fulvestrant, a non-steroidal aromatase inhibitor (anastrozole, letrozole), tamoxifen, and exemestane for first and subsequent line therapy. Faslodex (fulvestrant), an estrogen receptor antagonist, was approved by the FDA for the treatment of HR-positive, HER2-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy, HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy, HR-positive, HER2-negative advanced or metastatic breast cancer in postmenopausal women in combination with ribociclib as initial endocrine based therapy or following disease progression on endocrine therapy, and HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy.[7] Fulvestrant was approved in 2002. The serious risks associated with fulvestrant include risk of bleeding, increased exposure in patients with hepatic impairment, injection site reaction, embryo-fetal toxicity, and immunoassay measurement of serum estradiol. Fulvestrant does not have a boxed warning in its label and does not require a REMS to ensure the benefits outweighed the risks.

Tamoxifen also does not require a REMS to ensure the benefits outweighed the risks, but has a boxed warning for uterine malignancies and thromboembolic events.[8] In addition, anastrozole, letrozole, and exemestane do not have a boxed warning in their respective labels and do not require a REMS to ensure the benefits outweighed their risks.[9,10,11]

Activating mutations in the *ESR1* gene are a common cause of acquired tumor resistance to endocrine therapies, particularly aromatase inhibitors, in patients with ER+HER2- metastatic breast cancer.[4] It is estimated that approximately 20-40% of patients who have received an aromatase inhibitor for treatment of metastatic breast cancer will develop an *ESR1* mutation. There are currently no specific therapies approved by the FDA for the treatment of ER-positive, HER2 negative, *ESR1*-mutated metastatic breast cancer.

[d] 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.*

4. Benefit Assessment

The pivotal trial EMERALD (NCT 03778931) supporting this application for efficacy and safety consisted of a Phase 3, randomized, open-label, active-controlled study which evaluated elacestrant in postmenopausal women and men with ER+/HER2- advanced or metastatic breast cancer (N=478), with 228 patients having *ESR1* mutations.[1,4] Patients were randomized to elacestrant 345 mg orally once daily (N=239) or standard of care endocrine therapy (N=239), which included fulvestrant (N=165) or an aromatase inhibitor including anastrozole, letrozole, or exemestane (N=68). The primary endpoint was progression-free survival (PFS) in patients with *ESR1* mutations and in all subjects. The median PFS in patients with *ESR1* mutations was 3.8 months in the elacestrant group (95% CI 2.2 to 7.3) and 1.9 months in the fulvestrant or an aromatase inhibitor group (95% CI 1.9 to 2.1), hazard ratio 0.55 (95% CI 0.39 to 0.77), p = 0.0005. The median PFS in all subjects was 2.79 months in the elacestrant group and 1.91 months in the fulvestrant or an aromatase inhibitor group, hazard ratio 0.697 (95% CI 0.552 to 0.880), p = 0.0018. One of the secondary endpoints was overall survival (OS). The median OS in patients with *ESR1* mutations was 24.2 months in the elacestrant group and 23.5 months in the fulvestrant or an aromatase Inhibitor group, hazard ratio 0.9 (95% CI 0.63 to 1.30), p = not significant. The FDA clinical reviewer recommended that the indication be limited to the *ESR1* mutation population based on the currently available data. The FDA clinical reviewer stated that the PFS results in the intent-to-treat (ITT) population were driven by patients with *ESR1* mutations. A clinically meaningful PFS benefit was only demonstrated for patients in the *ESR1* mutation subpopulation, but not for patients in the *ESR1* mutation not detected subpopulation.[e]

5. Risk Assessment & Safe-Use Conditions

The safety of elacestrant was evaluated in a Phase 3 clinical trial EMERALD (NCT 03778931).[1,4,f] In the safety population, 237 patients received elacestrant and 230 patients received fulvestrant or an aromatase inhibitor. Discontinuation due to an adverse event occurred in 6% in the elacestrant group and 4.3% in the fulvestrant or an aromatase inhibitor group.[12] Common adverse reactions reported with elacestrant included musculoskeletal pain, nausea, increased cholesterol, increased aspartate aminotransferase, increased triglycerides, fatigue, decreased hemoglobin, vomiting, increased alanine aminotransferase, decreased sodium, increased creatinine, decreased appetite, diarrhea, headache, constipation, abdominal pain, hot flush, and dyspepsia. Although low severity, mainly Grades 1-2, the following gastrointestinal adverse reactions occurred more commonly in elacestrant group compared to

[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.*

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

the fulvestrant or an aromatase inhibitor group: nausea (35% vs 19%), vomiting (19% vs 9%), decreased appetite (15% vs 10%), and dyspepsia (10% vs 2.6%).

In study EMERALD, the applicant indicated 4 deaths were due to treatment emergent adverse event (TEAE) in the elacestrant group and 6 deaths were due to TEAE in the fulvestrant or an aromatase inhibitor group.[4] In the elacestrant group, 1 death was due to a cardiac arrest, 1 death was due to septic shock, 1 death was due to diverticulitis, and 1 death was due to an unknown cause.

The serious risks[g] associated with elacestrant which include dyslipidemia and embryo-fetal toxicity are summarized in the sections below.

5.1. Dyslipidemia

An adverse event of hypercholesterolemia and hypertriglyceridemia occurred in 30% of patients and 27% of patients receiving elacestrant, respectively. Grade 3 hypercholesterolemia was reported in 0.9% of patients and Grade 4 hypertriglyceridemia was reported in 2.2% of patients. The proposed label recommends to monitor lipid profile prior to starting and periodically while taking elacestrant. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.2. Embryo-Fetal Toxicity

Elacestrant may cause fetal harm based on animal studies and the mechanism of action of the drug. Elacestrant has been reported to cause adverse developmental outcomes including embryo-fetal mortality and structural abnormalities when administered to pregnant rats. The adverse developmental outcomes were reported at maternal exposures below the recommended dose based on area under the curve (AUC). No clinical data is available with elacestrant in pregnancy in humans. The risk of embryo-fetal toxicity will be included in a patient package insert and the warnings and precautions section of the label. The proposed label states to advise pregnant women and females of reproductive potential of the potential risk to a fetus. The proposed label recommends in females of reproductive potential to verify pregnancy status before starting elacestrant and that effective contraception be used during treatment and for 1 week after the last dose. In addition, in males with female partners of reproductive potential it is recommended that effective contraception be used during treatment and for 1 week after the last dose.

[g] 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.

6. Expected Postmarket Use

If approved, elacestrant will primarily be used in both inpatient and outpatient settings. The likely prescribers will be hematologists and oncologists.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for elacestrant beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The FDA clinical reviewer recommends approval of elacestrant on the basis of the efficacy and safety information currently available. Elacestrant is an estrogen receptor antagonist and, if approved, will be a treatment option for postmenopausal women or adult men, with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy. The efficacy of elacestrant was supported by the EMERALD study, in which in patients with *ESR1* mutations the elacestrant group had a median PFS of 3.8 months and the fulvestrant or an aromatase inhibitor group had a median PFS of 1.9 months, hazard ratio 0.55. The review team concluded that for patients in the *ESR1* mutation not detected subpopulation, the benefit-risk assessment for elacestrant was not favorable. Therefore, the indication will be limited to patients with *ESR1* mutations where the benefit risk was favorable.

The serious risks associated with elacestrant of dyslipidemia and embryo-fetal will be communicated in the warnings and precautions section of the label. Gastrointestinal toxicity was also noted as an important safety signal and although of lower grade, may require treatment with other medications and negatively impact quality of life. However, the review team considers these toxicities acceptable given that clinical benefit was demonstrated in patients with *ESR1* mutations.

Breast cancer is a common cause of cancer in women in the United States. The estimated number of women with metastatic breast cancer in the United States in 2017 was 154,794. Metastatic breast cancer is currently not curable and the five year relative survival of distant breast cancer is 30%. The likely prescribers will be hematologists and oncologists who should have experience managing the serious adverse events reported with elacestrant. If approved, based on the efficacy and risk associated with elacestrant for treatment of postmenopausal women or adult men, with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy, the DRM and DO1 recommendation is that a REMS is not necessary to ensure that the benefits outweigh the risks and the risks can be communicated using labeling.

9. Conclusion & Recommendations

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

10. Appendices

10.1. References

[1] Proposed prescribing information for elacestrant as currently edited by FDA, January 24, 2023.

[2] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Breast cancer (version 4.2022 – June 21, 2022). https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (accessed 2023 January 8).

[3] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72(1):7-33.

[4] Orserdu (elacestrant) multi-disciplinary review and evaluation. Accessed January 24, 2023.

[5] Mariotto AB, Etzioni R, Hurlbert M, Penberthy L, Mayer M. Estimation of the Number of Women Living with Metastatic Breast Cancer in the United States. Cancer Epidemiol Biomarkers Prev. 2017;26(6):809-815.

[6] Cancer Stat Facts: Female Breast Cancer. National Cancer Institute Surveillance, Epidemiology, and End Results Program. https://seer.cancer.gov/statfacts/html/breast.html (accessed 2023 January 8)

[7] Faslodex (fulvestrant) package insert. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2021 January.

[8] Soltamox (tamoxifen citrate) package insert. Raleigh, NC: Midatech Pharma US Inc., 2019 April.

[9] Arimidex (anastrozole) package insert. Baudette, MN: ANI Pharmaceuticals, Inc.; 2019 August.

[10] Femara (letrozole) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2020 May.

[11] Aromasin (exemestane) package insert. New York, NY: Pharmacia and Upjohn Company LLC A subsidiary of Pfizer Inc., 2021 November.

[12] Krol D, Lingam B, Gittleman H, Fiero M, Shah M. Division of Oncology 1 (DO1). Elacestrant. Mid-Cycle Meeting, clinical and statistics reviewer slides. October 6, 2022.

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