NEW DRUG APPROVAL

Brand Name	Orserdu™
Generic Name	elacestrant
Drug Manufacturer	Stemline Therapeutics, Inc

New Drug Approval

FDA Approval Date: January 27, 2023

Review Designation: Priority

Type of review: Type 1 - New Molecular Entity; New Drug Application (NDA): 217639

Dispensing restriction: Specialty; Limited Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Breast cancer is the most common cancer diagnosed in women, accounting for more than 1 in 10 new cancer diagnoses each year. It is the second most common cause of death from cancer among women in the world. Anatomically, the breast has milk-producing glands in front of the chest wall. They lie on the pectoralis major muscle, and there are ligaments support the breast and attach it to the chest wall. Fifteen to 20 lobes circularly arranged to form the breast. The fat that covers the lobes determines the breast size and shape. Each lobe is formed by lobules containing the glands responsible for milk production in response to hormone stimulation. Breast cancer always evolves silently. Most of the patients discover their disease during their routine screening. Others may present with an accidentally discovered breast lump, change of breast shape or size, or nipple discharge. However, mastalgia is not uncommon. Physical examination, imaging, especially mammography, and tissue biopsy must be done to diagnose breast cancer. The survival rate improves with early diagnosis. The tumor tends to spread lymphatically and hematologically, leading to distant metastasis and poor prognosis. This explains and emphasizes the importance of breast cancer screening programs.

Invasive breast cancer affects 1 in 8 women in the United States (12.4%) during their lifetime. In the United States, about 266,120 women will have invasive breast carcinoma in 2018, and 63,960 will have in situ breast cancer. In 2018, approximately 2550 men will have invasive breast cancer. Approximately 1 in 1000 men will have breast cancer during their lifetime. In the year 2000, the incidence of breast cancer in the United States began decreasing. This decrease may be due to the reduced use of hormone replacement therapy (HRT) by women. A connection was suggested between HRT and increased breast cancer risk. About 40,920 US women may die in 2018 from breast cancer. Larger decreases occur in women younger than 50 years old. In 2008, there were an estimated 1.38 million new cases of invasive breast cancer worldwide. The 2008 incidence of female breast cancer ranged from 19.3 cases per 100,000 in Eastern Africa to 89.9 cases per 100,000 in Western Europe. With early detection and significant advances in treatment, death rates from breast cancer have been decreasing over the past 25 years in North America and parts of Europe. In many African and Asian countries (e.g., Uganda, South Korea, and India), however, breast cancer death rates are rising. The incidence rate of breast cancer increases with age, from 1.5 cases per 100,000 in women 20 to 24 years of age to a peak of 421.3 cases per 100,000 in women 75 to 79 years of age; 95% of new cases occur in women aged 40 years or older. The median age of women at the time of breast cancer diagnosis is 61 years. According to the American Cancer Society (ACS), breast cancer rates among women from various racial and ethnic groups are as follows:

- Non-Hispanic white: 128.1 in 100,000
- African American: 124.3 in 100,000

- Hispanic/Latina: 91.0 in 100,000
- American Indian/Alaska Native: 91.9 in 100,000
- Asian American/Pacific Islander: 88.3 in 100,000

Efficacy

The efficacy of Orserdu™ was evaluated in EMERALD (NCT03778931), a randomized, open-label, active-controlled, multicenter trial that enrolled 478 postmenopausal women and men with ER+/HER2- advanced or metastatic breast cancer of which 228 patients had ESR1 mutations. Patients were required to have disease progression on one or two prior lines of endocrine therapy, including one line containing a CDK4/6 inhibitor. Eligible patients could have received up to one prior line of chemotherapy in the advanced or metastatic setting.

Patients were randomized (1:1) to receive Orserdu™ 345 mg orally once daily (n=239), or investigator's choice of endocrine therapy (n=239), which included fulvestrant (n=166), or an aromatase inhibitor (n=73; anastrozole, letrozole or exemestane). Randomization was stratified by ESR1 mutation status (detected vs not detected), prior treatment with fulvestrant (yes vs no), and visceral metastasis (yes vs no). ESR1 mutational status was determined by blood circulating tumor deoxyribonucleic acid (ctDNA) using the Guardant360 CDx assay and was limited to ESR1 missense mutations in the ligand binding domain (between codons 310 to 547). Patients were treated until disease progression or unacceptable toxicity.

The major efficacy outcome was progression-free survival (PFS), assessed by a blinded imaging review committee (BIRC). An additional efficacy outcome measure was overall survival (OS).

A statistically significant difference in PFS was observed in the intention to treat (ITT) population and in the subgroup of patients with ESR1 mutations. An exploratory analysis of PFS in the 250 (52%) patients without ESR1 mutations showed a HR 0.86 (95% CI: 0.63, 1.19) indicating that the improvement in the ITT population was primarily attributed to the results seen in the ESR1 mutated population.

Among the patients with ESR1 mutations (n=228), the median age was 63 years (range: 28-89); 100% were female; 72% were White, 5.7% Asian, 3.5% Black, 0.4% Other, 18.4% unknown/not reported; 8.8% were Hispanic/Latino; and baseline ECOG performance status was 0 (57%) or 1 (43%). Most patients had visceral disease (71%); 62% had received 1 line of endocrine therapy and 39% had received 2 lines of endocrine therapy in the advanced or metastatic setting. All patients had received prior treatment with a CDK4/6 inhibitor, 24% had received prior fulvestrant, and 25% had received prior chemotherapy in the advanced or metastatic setting.

Efficacy results are presented in Table 1 and Figure 1 for patients with ESR1 mutations.

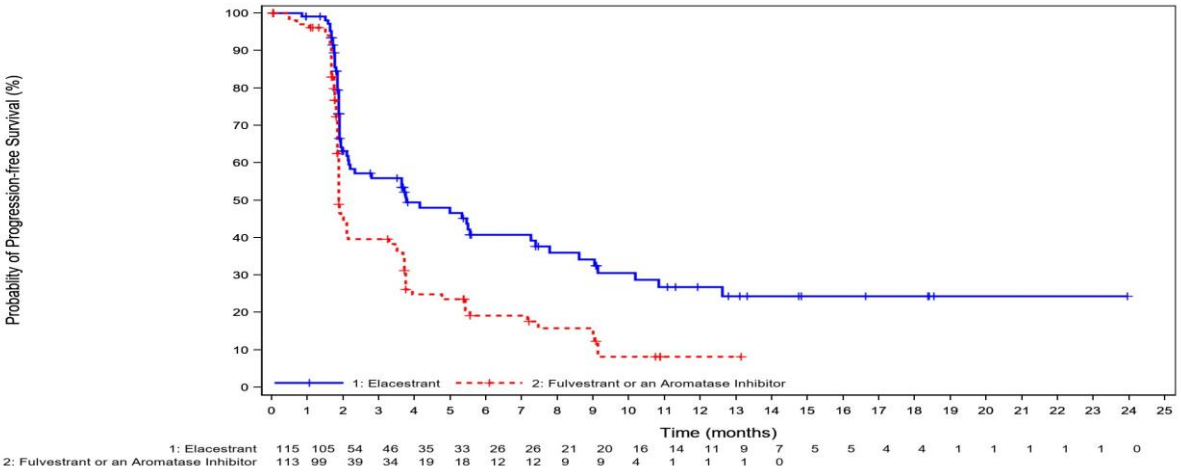
Table 1: Efficacy Results for EMERALD (Patients with ESR1 Mutations)

	Orserdu™ (N = 115)	Fulvestrant or an Aromatase Inhibitor (N=113)
Progression-free Survival (PFS)[a]		
Number of PFS Events, n (%)	62 (54)	78 (69)
Median PFS months[b] (95% CI)	3.8 (2.2, 7.3)	1.9 (1.9, 2.1)
Hazard ratio[c] (95% CI)	0.55 (0.39, 0.77)	
p-value[d]	0.0005	
Overall Survival (OS)		
Number of OS Events, n (%)	61 (53)	60 (53)
Hazard ratio[c] (95% CI)	0.90 (0.63, 1.30)	
p-valued	NS[e]	

CI=confidence interval; *ESR1*=estrogen receptor 1

[a] PFS results based on blinded imaging review committee.
[b] Kaplan-Meier estimate; 95% CI based on the Brookmeyer-Crowley method using a linear transformation.
[c] Cox proportional hazards model stratified by prior treatment with fulvestrant (yes vs no) and visceral metastasis (yes vs no).
[d] Stratified log-rank test two-sided p-value.
[e] NS – Not statistically significant.

Figure 1: Kaplan-Meier Curve for PFS in EMERALD (Patients with *ESR1* Mutations, BIRC Assessment)



[+] Censored times

The most common (>10%) adverse reactions, including laboratory abnormalities, of Orserdu™ were musculoskeletal pain, nausea, increased cholesterol, increased AST, increased triglycerides, fatigue, decreased hemoglobin, vomiting, increased ALT, decreased sodium, increased creatinine, decreased appetite, diarrhea, headache, constipation, abdominal pain, hot flush, and dyspepsia.

Safety

ADVERSE EVENTS

The safety of Orserdu™ was evaluated in 467 patients with ER+/HER2- advanced breast cancer following CDK4/6 inhibitor therapy in EMERALD, a randomized, open-label, multicenter study. Patients received Orserdu™ 345 mg orally once daily (n=237) or standard of care (SOC) consisting of fulvestrant or an aromatase inhibitor (n=230). Among patients who received Orserdu™, 22% were exposed for 6 months or longer and 9% were exposed for greater than one year.

Serious adverse reactions occurred in 12% of patients who received Orserdu™. Serious adverse reactions in >1% of patients who received Orserdu™ were musculoskeletal pain (1.7%) and nausea (1.3%). Fatal adverse reactions occurred in 1.7% of patients who received Orserdu™, including cardiac arrest, septic shock, diverticulitis, and unknown cause (one patient each).

Permanent discontinuation of Orserdu™ due to an adverse reaction occurred in 6% of patients. Adverse reactions which resulted in permanent discontinuation of Orserdu™ in >1% of patients were musculoskeletal pain (1.7%) and nausea (1.3%).

Dosage interruptions of Orserdu™ due to an adverse reaction occurred in 15% of patients. Adverse reactions which resulted in dosage interruption of Orserdu™ in >1% of patients were nausea (3.4%), musculoskeletal pain (1.7%), and increased ALT (1.3%).

Dosage reductions of Orserdu™ due to an adverse reaction occurred in 3% of patients. Adverse reactions which required dosage reductions of Orserdu™ in >1% of patients were nausea (1.7%).

The most common (>10%) adverse reactions, including laboratory abnormalities, of Orserdu™ were musculoskeletal pain, nausea, increased cholesterol, increased AST, increased triglycerides, fatigue, decreased hemoglobin, vomiting, increased ALT, decreased sodium, increased creatinine, decreased appetite, diarrhea, headache, constipation, abdominal pain, hot flush, and dyspepsia.

Table 2: Adverse Reactions (>10%) in Patients with ER-positive, HER2-negative, Advanced or Metastatic Breast Cancer Who Received Orserdu™ in EMERALD[a]

Adverse Reaction	Orserdu™ (n=237)		Fulvestrant or an Aromatase Inhibitor (n=230)	
	All Grades (%)	Grade 3 or 4 [c] (%)	All Grades (%)	Grade 3 or 4 [c] (%)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[b]	41	7	39	1
Gastrointestinal disorders				
Nausea	35	2.5	19	0.9
Vomiting[b]	19	0.8	9	0
Diarrhea	13	0	10	1
Constipation	12	0	6	0
Abdominal pain[b]	11	1	10	0.9
Dyspepsia	10	0	2.6	0
General disorders				
Fatigue[b]	26	2	27	1
Metabolism and nutrition disorders				
Decreased appetite	15	0.8	10	0.4
Nervous system				
Headache	12	2	12	0
Vascular disorders				
Hot flush	11	0	8	0

[a]Adverse reactions were graded using NCI CTCAE version 5.0.
[b]Includes other related terms
[c]Only includes Grade 3 adverse reactions.

Clinically relevant adverse reactions in < 10% of patients who received Orserdu™ included rash, insomnia, dyspnea, cough, dizziness, stomatitis and gastroesophageal reflux disease.

WARNINGS & PRECAUTIONS

Dyslipidemia
Hypercholesterolemia and hypertriglyceridemia occurred in patients taking Orserdu™ at an incidence of 30% and 27%, respectively. The incidence of Grade 3 and 4 hypercholesterolemia and hypertriglyceridemia were 0.9% and 2.2%, respectively.
Monitor lipid profile prior to starting and periodically while taking Orserdu™.

Embryo-Fetal Toxicity
Based on findings in animals and its mechanism of action, Orserdu™ can cause fetal harm when administered to a pregnant woman. Administration of elacestrant to pregnant rats resulted in adverse developmental outcomes, including embryo-fetal mortality and structural abnormalities, at maternal exposures below the recommended dose based on area under the curve (AUC).
Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Orserdu™ and for 1 week after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with Orserdu™ and for 1 week after the last dose.

CONTRAINDICATIONS

None reported.

Clinical Pharmacology

MECHANISMS OF ACTION

Elacestrant is an estrogen receptor antagonist that binds to estrogen receptor-alpha (ERα). In ERpositive (ER+) HER2-negative (HER2-) breast cancer cells, elacestrant inhibited 17β-estradiol mediated cell proliferation at concentrations inducing degradation of ERα protein mediated through proteasomal pathway. Elacestrant demonstrated in vitro and in vivo antitumor activity including in ER+ HER2- breast cancer models resistant to fulvestrant and cyclin-dependent kinase 4/6 inhibitors and those harboring estrogen receptor 1 gene (ESR1) mutations.

Dose & Administration

ADULTS

- Select patients for treatment based on the presence of ESR1 mutations.
- The recommended dosage of Orserdu™ is one 345 mg tablet taken orally, once daily.
- Dose interruption, reduction, or permanent discontinuation may be required due to adverse reactions.

PEDIATRICS

The safety and effectiveness of Orserdu™ in pediatric patients have not been established.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

None.

HEPATIC IMPAIRMENT

Avoid use of Orserdu™ in patients with severe hepatic impairment (Child-Pugh C). Reduce the Orserdu™ dosage to 258 mg once daily for patients with moderate hepatic impairment (Child-Pugh B). No dosage adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A)

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 345 mg and 86 mg