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Elacestrant (ORSERDU™)
Mini-Monograph
June 2023

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

FDA APPROVAL	**Description/MOA**	Estrogen receptor antagonist; inhibits 17β-estradiol-mediated cell growth; active in ER+, HER2-, *ESR1* mutation-positive advanced breast cancer
	Indication(s) Under Review	Treatment of ER+, HER2-, *ESR1*-mutated advanced or MBC after progression ≥ 1L endocrine therapy in men or postmenopausal women
	Dosage Form(s)	Oral tablets: 86 mg and 345 mg

CLINICAL EVIDENCE	**Study/Design**	EMERALD: Randomized, open-label, multicenter trial
	Population	N=478 [n=228 *ESR1*-mutated]; ER+, HER2- advanced or MBC after 1-2L prior endocrine tx (incl 1L CDK4/6i + AI or fulvestrant) or progression on/within 12 mos of adjuvant endocrine therapy; ECOG PS 0-1; Excluded: CV events in prior 6 mos*
	Demographics	mAge 63 yrs; women (~98%); white (~87.5%); Asian (8%); Hispanic (8%); visceral mets (~70%)
	Intervention	Randomized 1:1 to elacestrant 345 mg PO daily vs. SOC (Inv choice of fulvestrant or AI monotherapy, not used previously); Stratified by ESR1 mutation status, prior tx w/fulvestrant, visceral metastases
	Results	*ESR1*-mutated: PFS events: 54 vs. 69%; mPFS: 3.8 vs. 1.9 mos [HR 0.55 (0.39-0.77); p=0.0005] ITT pop'n w/o ESR1-mutation (52%): PFS [HR 0.86 (0.63-1.19)], so ITT PFS benefit due to *ESR1*-mutated pop'n; No significant difference in OS at interim analysis; trend favors elacestrant; Point estimates in subgroups favor elacestrant, confidence interval of prior treatment with fulvestrant crossed value = 1.0 [HR 0.67(95% CI 0.44-1.03)
	Summary	Significant PFS-benefit in those with *ESR1*-mutation; no benefit in those without; no OS difference noted

* CV events include: unstable angina, MI, CABG, prolonged QT interval, uncontrolled afib, NYHA > Class II heart failure, coagulopathy, CVA

SAFETY	**Boxed warnings**	None
	Contraindications	None
	Warnings/Precautions	Dyslipidemia, Embryo-fetal toxicity
	Adverse reactions	≥ 10%: musculoskeletal pain, nausea, ↑cholesterol, ↑AST, ↑trigs, fatigue, ↓hgb, vomiting, ↑ALT, ↓sodium, ↑SCr, ↓appetite, diarrhea, headache, constipation, abdominal pain, hot flush, dyspepsia
	Drug Interactions	Avoid moderate-strong CYP3A4 inducers/inhibitors; use caution with P-gp substrates and BCRP substrates as their concentration may increase along with AEs
	Other	Avoid in severe hepatic impairment (Child-Pugh C); dose-reduce in mod impairment

Drug and Alternatives	Formulary status	Clinical Guidance	Other Considerations
Elacestrant	TBD	None	Oral form taken with food; caution in hepatic impairment; ↑risk of dyslipidemia; avoid concomitant use with CYP3A4 inhibitors/inducers
Fulvestrant	PA-F Restrict to H/O	None	Initial doses IM on days 1, 15, 29, then monthly IM injections (250mg/5ml x2);
Aromatase Inhibitors	Formulary	None	AI (letrozole, anastrozole, exemestane) are oral formulations

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Projected Place in Therapy/Conclusions

- Among patients with *ESR1*-mutation, ER+, HER2- advanced breast cancer s/p endocrine therapy that included 1L with a CDK4/6 inhibitor, elacestrant improved PFS compared to SOC monotherapy with fulvestrant or AI
- Evaluate hepatic function, lipid profile and potential drug-drug interactions at baseline and throughout course of treatment
- Stress that patients should take daily dose with food to minimize GI distress

Key

AI aromatase inhibitor, ITT intent-to-treat, PFS progression-free survival, OS overall survival, CDK4/6i cyclin-dependent kinase 4/6 inhibitor, SOC standard of care, HR hormone receptor, HER2 human epidermal growth factor receptor 2, MBC metastatic breast cancer, ESR1 estrogen receptor 1 gene

References

- Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results from the Randomized Phase III EMERALD Trial. J Clin Oncol 2022; 40: 3246-3256.
- Elacestrant (ORSERDU) prescribing information. Stemline Therapeutics, Inc. New York, NY. January 2023.