

Imlunestrant (INLURIYO)

National Drug Mini-Monograph

August 2026

VA Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

SUMMARY OF PRESCRIBING INFORMATION

Description / MOA	Imlunestrant is an estrogen receptor (ER) antagonist that binds to ER α . In vitro, imlunestrant induces degradation of ER α , leading to inhibition of ER-dependent gene transcription and cellular proliferation in ER+ breast cancer cells.
Indication Under Review	Treatment of adults with ER+, HER2-negative, <i>ESR1</i> -mutated (<i>ESR1m</i>) advanced or metastatic breast cancer (MBC) with disease progression following at least one line of endocrine therapy. (ET)
Dosage Regimen	The recommended dosage is 400 mg orally once daily until progressive disease (PD) or unacceptable toxicity.
Dosage Forms	200 mg white, film-coated, capsule-shaped tablets
Boxed Warnings	None
Contraindications	None
Other Warnings	Embryo-Fetal Toxicity (EFT): Based on animal findings, imlunestrant can cause fetal harm. Advise patients of reproductive potential to use effective contraception during treatment and for 1 week after the last dose.
Most Common AEs ($\geq$ 10%)	Decreased hemoglobin, musculoskeletal pain, decreased calcium, decreased neutrophils, increased AST, fatigue, diarrhea, increased ALT, increased triglycerides, nausea, decreased platelets, constipation, increased cholesterol, and abdominal pain.
Drug Interactions	Strong CYP3A Inhibitors: Avoid concomitant use; if unavoidable, decrease the dosage of imlunestrant Strong CYP3A Inducers: Avoid concomitant use; if unavoidable, increase the dosage of imlunestrant P-gp or BCRP Substrates: Avoid concomitant use where minimal concentration changes may lead to serious adverse reactions, as imlunestrant inhibits these transporters.
Pregnancy	Advise of potential risk to a fetus. Verify pregnancy status prior to initiation.
Lactation	Advise not to breastfeed during treatment and for 1 week after the final dose.
Renal Impairment	Mild or Moderate: No clinically significant differences in PK. Severe: Effects on PK are unknown
Hepatic Impairment	Mild: No dosage modification recommended. Moderate to Severe: Reduce dosage to 200 mg once daily.

CLINICAL EVIDENCE SUMMARY

Trial	EMBER-3
Design	Randomized, multinational, open-label, active-controlled, phase 3 trial.
Primary Endpoint	Investigator-assessed PFS in the <i>ESR1</i> -mutated population; investigator-assessed PFS in the overall population (all patients); and investigator-assessed PFS of imlunestrant-abemaciclib versus imlunestrant monotherapy in concurrently randomized patients.
Population	874 adults with ER-positive, HER2-negative advanced or metastatic breast cancer who recurred or progressed during or after aromatase inhibitor therapy (alone or with a CDK4/6i).
Interventions	Patients were randomized (1:1:1) Imlunestrant 400 mg once daily (N=331, 37.9%); Investigator's choice of ET (fulvestrant or exemestane) (N=330, 37.8%); imlunestrant 400 mg once daily + abemaciclib 150 mg twice daily (N=213, 24.4%)
Efficacy Results	<p>Imlunestrant vs. ET in <i>ESR1</i>-mutated Subgroup (N=256): Primary: mPFS 5.5 mos (N=138, 53.9%) vs. 3.8 mos (N=118, 46.1%); HR 0.62 (95% CI, 0.46–0.82) P<0.001 Secondary: mOS 34.5 months (N=138, 53.9%) vs. 23.1 months (N=118, 46.1%); HR 0.60 (95% CI, 0.43–0.86) P=0.0043 ORR: 14.3% (N=112) vs. 7.7% (N=91)</p> <p>Imlunestrant vs. ET in overall population (N=661) mPFS 5.6 vs. 5.5 months; HR 0.87 (95% CI 0.72-1.04) P=0.12; statistical significance not met</p> <p>Imlunestrant + abemaciclib ITT vs. Imlunestrant ITT (Concurrent Randomization, N=426): Primary: mPFS 9.4 mos (N=213, 50.0%) vs. 5.5 mos (N=213, 50.0%) HR 0.57 (95% CI, 0.44–0.73) P<0.001 Updated: mPFS: 10.9 months vs. 5.5 months; HR 0.59 Secondary: mOS data immature; mOS not reached vs. 34.4 months; HR 0.82</p>

Safety Results	<ul style="list-style-type: none"> The safety profile of imlunestrant monotherapy was comparable to standard ET. Most adverse events were grade 1 or 2, and treatment DCs due to adverse events were infrequent (4.6% vs. 1.2% for ET). Based on the EMBER-3 safety population (N=327): Fatigue (23%) Diarrhea (22%) Nausea (17%) Musculoskeletal Pain (30%) Arthralgia (14%) The addition of abemaciclib increased the incidence of adverse events, consistent with its known safety profile. Diarrhea was the most common event with the combination (86% any grade, 8% $\geq$ grade 3), but it was manageable with dose adjustments or supportive care. Adverse events $\geq$ Grade 3: imlunestrant 17%; ET 20%; imlunestrant + abemaciclib 49%
Authors' Conclusions	Imlunestrant monotherapy significantly improved PFS compared to standard ET among patients with ESR1 mutations. Imlunestrant plus abemaciclib improved PFS over imlunestrant monotherapy regardless of ESR1 mutation status, providing an all-oral targeted treatment option.
Trial Limitations	EMBER-3 was open-label, which may introduce bias in reporting adverse events. There was no direct comparison between imlunestrant plus abemaciclib and the standard of fulvestrant plus abemaciclib. OS data are immature.

THERAPEUTIC ALTERNATIVES AND THEIR PLACE IN THERAPY				
DRUG	VANF	VA Restrictions	FDA Labeling and/or Pertinent Clinical Outcomes	Guidelines/ Pathways
Imlunestrant MOA: oral SERD	TBD	TBD	EMBER-3: imlunestrant vs. fulvestrant or exemestane in ESR1m+ mPFS 5.5 vs. 3.8 mos; HR 0.62; p=0.0008 @ 28.5 mos, mOS 34.5 vs. 23.1 mos; HR 0.60; prespecified significance boundary was not reached <ul style="list-style-type: none"> Take on empty stomach Dose-reduce in mod-severe hepatic impairment Warnings/precautions include EFT 	NCCN "other recommended"; category 2A; PD on/after prior line AI +/- CDK4/6i in adjuvant or metastatic setting
Elacestrant MOA: oral SERD	PA-F	CFU	EMERALD, P3, elacestrant vs. SOC ET in ESR1m+ mPFS 3.8 vs. 1.9 mos; HR 0.55; p=0.0005 mOS HR 0.90 (95% CI 0.63-1.30) NS In ET + CDK4/6i, mPFS 8.6 vs. 1.9 mos <ul style="list-style-type: none"> Take with food Avoid in severe hepatic impairment Warnings/precautions include dyslipidemia, EFT 	NCCN "other recommended"; category 2A; PD on/after prior line AI + CDK4/6i in adjuvant or metastatic setting VA Breast Cancer Pathway v2.2026 <i>ESR1m</i> + directs to elacestrant
Vepdegestrant MOA: PROTAC ER degrader	NF (pending review)	TBD	VERITAC-2: vepdegestrant vs. fulvestrant in ESR1m mPFS 5.0 vs. 2.1 mos; HR 0.58; P<0.001 mOS data immature	NCCN "other recommended"; category 2A; PD after $\geq$ 1 line ET + CDK4/6i in metastatic setting

TBD to be determined; MOA mechanism of action; SERD selective estrogen receptor degrader; PROTAC proteolysis-targeting chimera; ER estrogen receptor; EFT embryo fetal toxicity; PD progressive disease; AI aromatase inhibitor; ET endocrine therapy; mPFS median progression-free survival; mOS median overall survival

POTENTIAL PLACE IN THERAPY

Summary of Evidence and Potential Place-in-Therapy	<ul style="list-style-type: none"> Imlunestrant is an oral SERD with FDA approval in HR+, HER2- advanced or metastatic breast cancer <ul style="list-style-type: none"> It is positioned as Category 2A, Other Recommended within NCCN in <i>ESR1</i>+ population, similar to elacestrant. VA Breast Cancer Pathway includes elacestrant in this space. Both improve PFS, and although imlunestrant appeared to have an improvement in OS, this did not meet the prespecified significance boundary. Differences in study population: <ul style="list-style-type: none"> Elacestrant was studied in a CDK4/6i-treated pop'n; CDK4/6i's were not mandated with imlunestrant. EMBER-3 also investigated imlunestrant + abemaciclib with positive PFS results in the overall pop'n (not <i>ESR1m</i> only), although this was not part of the FDA-approved labeling. Additional differences are noted in adverse event profile, how drug should be taken and hepatic dysfunction. Imlunestrant causes more diarrhea (22%), fatigue (23%) with hypercholesterolemia (10%), but does not have dyslipidemia as a labeled warning. Imlunestrant is taken on an empty stomach: elacestrant is taken with food to minimize GI irritation. Imlunestrant should be dose-reduced in severe hepatic impairment; elacestrant should be avoided.
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References

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