New Drug Overview

Veppanu (vepdegestrant)
PDL Category: Antineoplastics

Introduction

Disease Background:

- Breast cancer is the most common malignancy diagnosed worldwide in women, with reports of more than 2 million cases yearly. In addition, globally, more deaths are reported from this cancer than any other cancer in women (*Joe 2026*).
  - It is the most common cancer in women in the United States, and the second leading cause of cancer death in women.
- Breast cancer, a malignancy of the breast tissue, is characterized as either carcinoma in situ or invasive breast cancer (*Henry et al 2026*).
  - Carcinoma in situ is also known as noninvasive carcinoma and is stage 0. This is defined as cancer cells that have not occupied outside of the basement membrane of the duct or lobule.
  - Invasive breast cancer is categorized as early breast cancer, locally advanced breast cancer, or advanced (metastatic) breast cancer.
    - Early breast cancer includes stages I, IIA, and IIB, with no extension of tumor to the chest wall or skin and no distant metastases. There may be ipsilateral axillary lymph node metastases.
    - Locally advanced breast cancer includes stages IIIA, IIIB, and IIIC, with metastases in the ipsilateral axillary lymph nodes and internal mammary lymph nodes. Tumor size is greater than 5 cm and with direct extension to the chest wall or skin. There is no distant metastases.
    - Advanced (metastatic) breast cancer includes stage IV tumors with disease that goes beyond the breast and axilla. Sites that are frequently metastasized include the bone, liver, lung and brain.
- In areas where there are recognized breast cancer screening programs, patients are generally asymptomatic when diagnosed. Nevertheless, diagnosis occurs in up to 15 percent of women because of clinical signs (eg, breast mass, nipple discharge, skin changes, axillary adenopathy, or other changes in the breast) that are not found during mammogram testing. This is known as mammographically occult disease. In addition, about 30 percent exhibit a breast mass found in between mammograms, known as interval cancers (*Joe 2026*).
- Upon diagnosis, it is essential for breast cancers to be tested for estrogen (ER) and progesterone (PR) receptor expression and for overexpression of human epidermal growth factor 2 (HER2) receptors. This is crucial for prognostic and therapeutic reasons (*Joe 2026*).
  - ER and PR are predictive for invasive breast cancer.
  - Data from a study that included 61,309 cases of breast cancer diagnosed between 1999 and 2004 suggested the following proportions with various receptor phenotypes:
    - Hormone receptor positive cancers (ER and/or PR) accounted for most cases, approximately 80%.
    - HER2 was overexpressed in 23%; of these, 67% were hormone receptor-positive and 32% were hormone receptor-negative.
    - Triple negative cancers (ER, PR, and HER2-negative) accounted for about 13%.
  - The most frequent subtype of breast cancer is ER+, HER2- (*Jhaveri et al 2025*).
- Knowing the stage and subtype (ER, PR, HER2) assists in the management of breast cancer (*Henry et al 2026, Joe 2026*).
- Veppanu was FDA approved in 2026.

Pharmacology/Usage

- Veppanu (vepdegestrant) is a heterobifunctional protein degrader that binds to estrogen receptor (ER) and the E3 ligase cereblon (CRBN). This interaction results in the degradation cascade through CRBN-mediated polyubiquitination and degradation of ER by the proteasome, leading to reduction of ER protein levels in breast cancer cells.

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- Vepdegestrant induced degradation of wild-type (WT) and mutant ER, inhibited ER-dependent breast cancer cell line proliferation *in vitro* and demonstrated antitumor activity *in vivo* in both WT and mutant *ESR1* breast cancer models.

Indications

Table 1. Food and Drug Administration Approved Indications

Indication	Veppanu (vepdegestrant)
• 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, as detected by an FDA-authorized test, with disease progression following at least one line of endocrine therapy.	✔

(Prescribing information: Veppanu 2026)

- Information on indications, mechanism of action, pharmacokinetics, dosing, safety, and clinical efficacy summary has been obtained from the prescribing information for the individual products, except where noted otherwise.

Dosing and administration

Table 2. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Veppanu (vepdegestrant)	Film-Coated Tablets: 100mg and 200mg. -Swallow whole; do not chew, crush, dissolve, or split prior to swallowing. Do not take if tablets are broken, cracked, or look damaged.	PO	Take 200mg PO QD with food until disease progression or unacceptable toxicity.	• Select patients for treatment of ER-positive, HER2-negative advanced or metastatic breast cancer based on the presence of *ESR1* mutation(s) in plasma specimen using an FDA-authorized test. Information on FDA-authorized tests for detection of *ESR`1* mutations in breast cancer is available online. • If a patient misses a dose or vomits after taking a dose, the patient should take the next dose at the regularly scheduled time.

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Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				• There are dosage modification recommendations for adverse reactions.

See the current prescribing information for full details.

Clinical Efficacy Summary

- The efficacy of Veppanu was assessed in VERITAC-2, a randomized, open-label, active-controlled, multicenter trial that enrolled adults (N=624) with ER-positive, HER2-negative, advanced or metastatic breast cancer, of whom 270 patients had tumors carrying *ESR1* mutations.
  - Patients were required to have disease progression on 1 to 2 prior lines of endocrine therapy, including 1 line with a CDK4/6 inhibitor. Progression during or within 12 months from the end of adjuvant therapy was counted as 1 line of endocrine therapy for advanced/metastatic setting.
  - Pre-menopausal and perimenopausal women and men received a gonadotropin-releasing hormone (GnRH) agonist.
  - Patients were excluded if they had received chemotherapy for advanced or metastatic disease or fulvestrant in any line of therapy, or if progression on the most recent line of endocrine therapy occurred within the first 6 months.
  - Patients were randomized to receive Veppanu 200mg QD (N = 313) or fulvestrant 500mg IM on days 1 and 15 of cycle 1 and then QM thereafter (N = 311).
    - Patients were treated until disease progression or unacceptable toxicity.
  - Of the patients whose tumors had *ESR1* mutations (N=270), the median age was 60 years (range 26 to 87), while 47% were White and all but 1 were female. Of the 269 women, 20% were pre/perimenopausal. Baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 (57%) or 1 (43%). Most patients (68%) had visceral disease; 81% had received 1 line of endocrine therapy and 19% had received 2 lines of endocrine therapy in the advanced or metastatic setting. All patients had received prior treatment with a CDK4/6 inhibitor.
  - The major efficacy outcome was progression-free survival (PFS) as assessed by blinded independent central review (BICR) in the population of patients whose tumors had an *ESR1* mutation and in the overall population assessed per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
    - Additional efficacy outcomes were overall survival (OS) and objective response rate (ORR) as assessed by BICR.
      - A statistically significant difference in PFS by BICR was observed for the patients whose tumors had *ESR1* mutations for Veppanu compared with fulvestrant.
      - Overall survival was immature with 16% of deaths in this population at the time of the PFS analysis.
      - Results are presented in the table below, which was adapted from the prescribing information.

Table 3. Efficacy results

(Patients with ESR1-mutated tumors)	Veppanu (N = 136)	Fulvestrant (N = 134)
Progression-free Survival (PFS)		
Number of events (%)	79 (58%)	95 (71%)
Median in months	5.0	2.1
Hazard ratio; p-value	0.57; p = 0.0001	

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(Patients with ESR1-mutated tumors)	Veppanu (N = 136)	Fulvestrant (N = 134)
Confirmed Objective Response Rate (ORR)		
Patients with measurable disease	97	100
ORR	19%	4%
Complete response rate	0%	0%
Partial response rate	19%	4%

Clinical guidelines

- **National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Breast Cancer** (*NCCN 2026*).
  - NCCN guidelines were updated in 2026 and includes vepdegestrant.
    - Vepdegestrant has been added to the list of targeted therapies for recurrent unresectable (local or regional) or Stage IV disease for invasive breast cancer. It is listed as category 2A for NCCN category of evidence for HR-positive/HER2-negative breast cancer subtype with *ESR1* mutation biomarker. The NCCN category of preference for vepdegestrant is listed as other recommended option (rather than some are listed as preferred). There is also a note that indicates it is for disease progression after at least one line of endocrine therapy + CDK 4/6 inhibitor in the metastatic setting.

Safety summary

- **Contraindications:** None.

- **Box Warning:** None.

- **Warnings and precautions:**
  - Veppanu can cause QT (QTc) interval prolongation.
    - Correct electrolyte abnormalities, including hypokalemia and hypomagnesemia, prior to and during treatment with Veppanu. Perform an ECG prior to initiation of treatment with Veppanu and do not initiate Veppanu in patients with QTc > 470 msec. Repeat ECG about 4 weeks after starting treatment and as clinically indicated.
    - In patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval, additional ECG monitoring may be needed.
    - Avoid concomitant use of Veppanu with strong CYP3A inhibitors or drugs known to prolong the QTc interval. Reduce Veppanu dose when concomitant use with strong CYP3A inhibitors cannot be avoided. If concomitant use with other QTc-prolonging agents cannot be avoided, increase the frequency of ECG monitoring.
    - Withhold, reduce dose, or permanently discontinue based on severity.
  - There is a warning regarding embryo-fetal toxicity, which is discussed in the special populations section.

- **Common adverse drug reactions**:
  - Listed % incidence for adverse drug reactions= reported % incidence for drug (Veppanu) minus reported % incidence for fulvestrant for all grades. Please note that an incidence of 0% means the incidence was the same as or less than comparator.

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- The most frequently reported adverse events included musculoskeletal pain (7%), fatigue (13%), nausea (5%), constipation (6.7%), decreased appetite (6%), and electrocardiogram QT prolonged (8.7%).

○ Listed % incidence for adverse drug reactions= reported % incidence for drug (Veppanu) minus reported % incidence for fulvestrant for all grades of laboratory abnormalities. Please note that an incidence of 0% means the incidence was the same as or less than comparator.

- The most frequently reported laboratory abnormalities included white blood cells decreased (18%), hemoglobin decreased (4%), neutrophils decreased (10%), platelets decreased (0%), aspartate aminotransferase increased (8%), alanine aminotransferase increased (0%), alkaline phosphatase increased (0%), blood potassium decreased (8%), and bilirubin increased (6%).

- **Drug interactions:**
  - ○ Vepdegestrant is a CYP3A substrate.
    - Avoid concomitant use of Veppanu with strong CYP3A inhibitors in patients receiving Veppanu 200mg QD. If concomitant use cannot be avoided, reduce Veppanu dosage.
    - Avoid concomitant use with strong CYP3A inhibitors in patients receiving Veppanu 100mg QD.
    - Avoid concomitant use with strong CYP3A inducers in patients receiving Veppanu 200mg QD. If concomitant use cannot be avoided, increase Veppanu dosage.
    - Avoid concomitant use with strong CYP3A inducers in patients receiving Veppanu 100mg QD.
  - ○ Vepdegestrant is a P-gp inhibitor.
    - Avoid concomitant use with certain P-gp substrates where minimal increases in concentration may lead to serious adverse reactions.
  - ○ Vepdegestrant is a UGT1A9 inhibitor.
    - Refer to the prescribing information for UGT1A9 substrates where minimal increases in the concentration may lead to serious adverse reactions.
  - ○ Vepdegestrant causes QTc interval prolongation.
    - Avoid concomitant use of Veppanu with other drugs with a known potential to prolong the QTc interval. If concomitant use cannot be avoided:
      - Obtain ECGs when initiating and during concomitant use, and as clinically indicated.
      - Withhold Veppanu if the QTc interval is > 480 ms or the change from baseline is > 60 ms.

- **Special populations:**
  - ○ There is no pregnancy category for this medication; however, the risk summary indicates that based on findings in animals and its mechanism of action, Veppanu can cause fetal harm when administered to a pregnant woman. There are no available human data on use in pregnant women to inform the drug-associated risk. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.
    - Verify the pregnancy status in females of reproductive potential prior to starting Veppanu treatment.
    - Advise females of reproductive potential to use effective contraception during treatment with Veppanu and for 2 weeks after the last dose.
    - Advise male patients with female partners of reproductive potential to use effective contraception during treatment with Veppanu and for 2 weeks after the last dose.
  - ○ The safety and efficacy of use in the pediatric population have not been established.

Conclusion

- Breast cancer is the most common malignancy diagnosed worldwide in women, with reports of more than 2 million cases yearly. In addition, globally, more deaths are reported from this cancer than any other cancer in women (*Joe 2026*).

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- It is the most common cancer in women in the United States, and the second leading cause of cancer death in women.
- Veppanu is a heterobifunctional protein degrader indicated for the treatment of adults with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer, as detected by an FDA-authorized test, with disease progression following at least one line of endocrine therapy.
- Veppanu can cause QT (QTc) interval prolongation.
  - Avoid concomitant use of Veppanu with strong CYP3A inhibitors or drugs known to prolong the QTc interval. Reduce Veppanu dose when concomitant use with strong CYP3A inhibitors cannot be avoided. If concomitant use with other QTc-prolonging agents cannot be avoided, increase the frequency of ECG monitoring.
- The efficacy of Veppanu was assessed in a randomized, open-label, active controlled trial that included adults (N = 624) with ER-positive, HER2-negative, advanced or metastatic breast cancer, of whom 270 patients had tumors carrying *ESR1* mutations. Patients were required to have disease progression on 1 to 2 prior lines of endocrine therapy, including 1 line with a CDK4/6 inhibitor.
  - The major efficacy outcome was progression-free survival (PFS), and results suggested a statistically significant difference in PFS was observed for the patients whose tumors had *ESR1* mutations for Veppanu compared with fulvestrant.
- NCCN guidelines have been updated to include Veppanu (vepdegestrant) and it is listed as a category 2A for NCCN category of evidence, being an option after prior lines of treatment.

- It is recommended that Veppanu should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.
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- **PDL Placement:**

☐ Recommended
☒ Non-Recommended with Conditions

References

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