BlueCross BlueShield
Federal Employee Program

# ENHERTU
# (fam-trastuzumab deruxtecan-nxki)

## RATIONALE FOR INCLUSION IN PA PROGRAM

### Background

Enhertu (fam-trastuzumab deruxtecan-nxki) is a HER2-directed antibody and topoisomerase inhibitor conjugate. The antibody is a humanized anti-HER2 IgG1. The small molecule, DXd, is a topoisomerase I inhibitor attached to the antibody by a cleavable linker. Following binding to HER2 on tumor cells, Enhertu is thought to undergo internalization and intracellular linker cleavage by lysosomal enzymes. Upon release, the membrane-permeable DXd is thought to cause DNA damage and apoptotic cell death (1).

### Regulatory Status

FDA-approved indications: Enhertu is indicated for the treatment of: (1)

- adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH positive) breast cancer who have received a prior anti-HER2-based regimen either:
    - in the metastatic setting, or
    - in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy.
- adult patients with unresectable or metastatic
    - Hormone receptor (HR)-positive, HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer, as determined by an FDA-approved test, that has progressed on one or more endocrine therapies in the metastatic setting.
    - HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by and FDA-approved test, who have received a prior chemotherapy in the metastatic setting; or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.
- adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.
- adult patients with locally advanced or metastatic HER2-positive (IHC 3+ or IHC 2+/ISH positive) gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen.

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- adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

Enhertu has a boxed warning regarding interstitial lung disease (ILD) and pneumonitis. Patients should be monitored for and promptly investigated for signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Enhertu should be permanently discontinued in all patients with Grade 2 or higher ILD/pneumonitis (1).

Enhertu also has a boxed warning regarding embryo-fetal harm during pregnancy. Patients should be advised of these risks and the need for effective contraception (1).

Severe neutropenia, including febrile neutropenia, can occur in patients treated with Enhertu. Patient's complete blood counts should be monitored prior to initiation, prior to each dose, and as clinically indicated. Based on the severity of neutropenia, Enhertu may require dose interruption or reduction (1).

Patients treated with Enhertu may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) should be assessed prior to initiation and at regular intervals during treatment as clinically indicated. LVEF decrease should be managed through treatment interruption. Enhertu should be permanently discontinued if a LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed. Enhertu should be permanently discontinued in patients with symptomatic congestive heart failure (CHF) (1).

The safety and effectiveness of Enhertu in pediatric patients less than 18 years of age have not been established (1).

**Summary**

Enhertu (fam-trastuzumab deruxtecan-nxki) is a HER2-directed antibody and topoisomerase inhibitor conjugate. Enhertu is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer, unresectable or metastatic HER2-low breast cancer, unresectable or metastatic HER2-ultralow breast cancer, unresectable or metastatic non-small cell

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lung cancer (NSCLC), locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma, and unresectable or metastatic HER2-positive solid tumors. Enhertu has a boxed warning regarding interstitial lung disease and embryo-fetal toxicity. Enhertu also has warnings for neutropenia and left ventricular dysfunction. The safety and effectiveness of Enhertu in pediatric patients less than 18 years of age have not been established (1).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of Enhertu while maintaining optimal therapeutic outcomes.

**References**

1. Enhertu [package Insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc.; January 2025.
2. NCCN Drugs & Biologics Compendium® Fam-trastuzumab deruxtecan-nxki 2025. National Comprehensive Cancer Network, Inc. Accessed on February 3, 2025.