

5.21.138

Section:	Prescription Drugs	Effective Date:	June 19, 2026
Subsection:	Antineoplastic Agents	Original Policy Date:	January 20, 2020
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Last Review Date: March 6, 2026

Enhertu

Description

Enhertu (fam-trastuzumab deruxtecan-nxki)

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 a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for: (1)

HER2-Positive Early Breast Cancer

- As neoadjuvant treatment of adult patients with HER2-positive (IHC 3+ or ISH+) Stage II or III breast cancer, as determined by an FDA-authorized test followed by a taxane, trastuzumab, and pertuzumab (THP)
- As adjuvant treatment of adult patients with HER2-positive (IHC 3+ or ISH+) breast cancer who have residual invasive disease following neoadjuvant trastuzumab (with or without pertuzumab) and taxane-based treatment

HER2-Positive Metastatic Breast Cancer

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- In combination with pertuzumab as first-line treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer as determined by an FDA-authorized test
- As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) 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.

HER2-Low and HER2-Ultralow Metastatic Breast Cancer

- As monotherapy for the treatment of 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-authorized test, that has progressed on one or more endocrine therapies in the metastatic setting.
- As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-authorized test, who have received a prior chemotherapy in the metastatic setting; or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

HER2-Mutant Unresectable or Metastatic Non-Small Cell Lung Cancer

- As monotherapy for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-authorized test, and who have received a prior systemic therapy.

HER2-Positive Locally Advanced or Metastatic Gastric Cancer

- As monotherapy for the treatment of 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.

HER2-Positive (IHC 3+) Unresectable or Metastatic Solid Tumors

- As monotherapy for the treatment of 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).

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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).

Related policies

Herceptin Hylecta, Kadcyla, Margenza, Nerlynx, Perjeta, Phesgo, Trastuzumab, Tukysa, Tykerb

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Enhertu may be considered **medically necessary** if the conditions indicated below are met.

Enhertu may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 18 years of age or older

Diagnoses

Patient must have **ONE** of the following:

1. HER2-positive early breast cancer **AND ONE** of the following:
 - a. Used as neoadjuvant treatment
 - i. HER2-positive (IHC3+ or ISH+) Stage II or III breast cancer, as determined by an FDA-authorized test

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- ii. Treatment will be followed by a taxane, trastuzumab, and pertuzumab (THP)
- b. Used as adjuvant treatment
 - i. HER2-positive (IHC3+ or ISH+) breast cancer who have residual invasive disease following neoadjuvant trastuzumab and taxane-based treatment
- 2. Unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer **AND ONE** of the following:
 - a. Used as first-line treatment
 - i. Used in combination with pertuzumab
 - ii. HER2-positive (IHC 3+ or ISH+) as determined by an FDA-authorized test
 - b. Patient has received a prior anti-HER2-based regimen in the metastatic setting
 - i. Used as monotherapy
 - c. Patient has received a prior anti-HER2-based regimen in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy
 - i. Used as monotherapy
- 3. Unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer
 - a. HER2-low (IHC 1+ or IHC 2+/ISH-) as determined by an FDA-authorized test
 - b. Used as monotherapy
 - c. Patient has **ONE** of the following:
 - i. Patient has received prior chemotherapy in the metastatic setting
 - ii. Patient developed disease recurrence during or within 6 months of completing adjuvant chemotherapy
 - iii. Patient is hormone receptor (HR)-positive and has progressed on one or more endocrine therapies in the metastatic setting
- 4. Unresectable or metastatic HER2-ultralow (IHC 0 with membrane staining) breast cancer
 - a. HER2-ultralow (IHC 0 with membrane staining) as determined by an FDA-authorized test
 - b. Patient is hormone receptor (HR)-positive and has progressed on one or more endocrine therapies in the metastatic setting
 - c. Used as monotherapy

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5. Unresectable or metastatic non-small cell lung cancer (NSCLC)
 - a. Tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-authorized test
 - b. Patient has received a prior systemic therapy
 - c. Used as monotherapy
6. Locally advanced or metastatic HER2-positive (IHC 3+ or IHC 2+/ISH positive) gastric or gastroesophageal junction adenocarcinoma
 - a. Patient has received a prior trastuzumab-based regimen
 - b. Used as monotherapy
7. Unresectable or metastatic HER2-positive (IHC 3+) solid tumor
 - a. Patient has received prior systemic treatment
 - b. **NO** satisfactory alternative treatment options
 - c. Used as monotherapy

AND ALL of the following:

1. Prescriber agrees to monitor for signs and symptoms of interstitial lung disease (ILD)
2. Prescriber agrees to monitor complete blood counts prior to initiation, prior to each dose, and as clinically indicated
3. Prescriber agrees to assess left ventricular ejection fraction (LVEF) prior to initiation and at regular intervals during treatment as clinically indicated
4. Females of reproductive potential **only**: patient has had a negative pregnancy test **AND** patient will be advised to use effective contraception during treatment with Enhertu and for 7 months after the last dose
5. Male patients with female partners of reproductive potential **only**: patient will be advised to use effective contraception during treatment with Enhertu and for 4 months after the last dose

Prior – Approval *Renewal* Requirements

Age 18 years of age or older

Diagnoses

Patient must have **ONE** of the following:

1. Unresectable or metastatic HER2-positive (IHC 3+ or ISH positive) breast cancer
 - a. Used as monotherapy **OR** in combination with pertuzumab

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2. Unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer
 - a. Used as monotherapy
3. Unresectable or metastatic HER2-ultralow (IHC 0 with membrane staining) breast cancer
 - a. Used as monotherapy
4. Unresectable or metastatic non-small cell lung cancer (NSCLC)
 - a. Used as monotherapy
5. Locally advanced or metastatic HER2-positive (IHC 3+ or IHC 2+/ISH positive) gastric or gastroesophageal junction adenocarcinoma
 - a. Used as monotherapy
6. Unresectable or metastatic HER2-positive (IHC 3+) solid tumor
 - a. Used as monotherapy

AND ALL of the following:

1. **NO** disease progression or unacceptable toxicity
2. Prescriber agrees to monitor for signs and symptoms of interstitial lung disease (ILD)
3. Prescriber agrees to monitor complete blood counts prior to each dose and as clinically indicated
4. Prescriber agrees to assess left ventricular ejection fraction (LVEF) at regular intervals during treatment as clinically indicated
5. Females of reproductive potential **only**: patient will be advised to use effective contraception during treatment with Enhertu and for 7 months after the last dose
6. Male patients with female partners of reproductive potential **only**: patient will be advised to use effective contraception during treatment with Enhertu and for 4 months after the last dose

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Duration 12 months

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Prior – Approval *Renewal* Limits

Same as above*

***NO** renewal for HER-2 positive early breast cancer

Rationale

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 HER2-positive early breast cancer, 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 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.; May 2026.
2. NCCN Drugs & Biologics Compendium[®] Fam-trastuzumab deruxtecan-nxki 2026. National Comprehensive Cancer Network, Inc. Accessed on January 29, 2026.

Policy History

Date	Action
January 2020	Addition to PA
March 2020	Annual review
June 2020	Annual review
September 2020	Annual review
December 2020	Annual review
February 2021	Addition of indication: HER2-positive gastric or gastroesophageal junction adenocarcinoma
March 2021	Annual review

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June 2021	Annual editorial review and reference update
March 2022	Annual review and reference update
May 2022	Per PI update, revised breast cancer indication to require a prior anti-HER2-based regimen either in the metastatic setting or in the neoadjuvant or adjuvant setting and developed disease recurrence during or within six months of completing therapy
June 2022	Annual review
August 2022	Per PI update, addition of indications: unresectable or metastatic HER2-low breast cancer and unresectable or metastatic NSCLC
September 2022	Annual review and reference update
November 2022	Per PI update, added initiation requirement for an FDA-approved test for HER2-low breast cancer
March 2023	Annual review and reference update
June 2023	Annual review and reference update
March 2024	Annual review and reference update
May 2024	Per PI update, added indication of HER2-positive solid tumors and added IHC/ISH stipulations to breast cancer and gastric cancer indications
June 2024	Annual review and reference update
March 2025	Annual editorial review and reference update. Added initiation requirement for female patients of reproductive potential to have a negative pregnancy test
April 2025	Per PI update, added indication of HR-positive, HER2-low or HER2-ultralow with progression on one or more endocrine therapies in the metastatic setting
June 2025	Annual review and reference update
December 2025	Per PI update, added indication of HER-2 positive breast cancer as first-line treatment in combination with pertuzumab. Also added monotherapy requirement for all other indications
March 2026	Annual review and reference update
June 2026	Per PI update, added indication of HER2-positive early breast cancer and also changed FDA-approved to FDA-authorized

Keywords

This policy was effective with interim approval on June 19, 2026 and will be reviewed by the FEP® Pharmacy and Medical Policy Committee on September 17, 2026.