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Section:	Prescription Drugs	**Effective Date:**	July 1, 2023
Subsection:	Antineoplastic Agents	**Original Policy Date:**	January 20, 2020
Subject:	Enhertu	**Page:**	1 of 6

Last Review Date: June 15, 2023

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 indicated for the treatment of: (1)

- adult patients with unresectable or metastatic HER2-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 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 gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen.

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).

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. Unresectable or metastatic HER2-positive breast cancer **AND ONE** of the following:
    a. Patient has received a prior anti-HER2-based regimen in the metastatic setting
    b. 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
2. 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-approved test
    b. 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
3. Unresectable or metastatic non-small cell lung cancer (NSCLC)
    a. Tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test
    b. Patient has received a prior systemic therapy
4. Locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma
    a. Patient has received a prior trastuzumab-based regimen

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 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 breast cancer
2. Unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer
3. Unresectable or metastatic non-small cell lung cancer (NSCLC)
4. Locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma

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

Prior – Approval *Renewal* Limits

Same as above

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 unresectable or metastatic HER2-positive breast cancer, unresectable or metastatic HER2-low breast cancer, unresectable or metastatic non-small cell lung cancer (NSCLC), and locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma. 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.; November 2022.
2. NCCN Drugs & Biologics Compendium® Fam-trastuzumab deruxtecan-nxki 2023. National Comprehensive Cancer Network, Inc. Accessed on April 11, 2023.

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
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

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 15, 2023 and is effective on July 1, 2023.