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Section:	Prescription Drugs	**Effective Date:**	April 1, 2021
Subsection:	Antineoplastic Agents	**Original Policy Date:**	January 20, 2020
Subject:	Enhertu	**Page:**	1 of 5

Last Review Date: March 12, 2021

Enhertu

Description

Enhertu (fam-trastuzumab deruxtecan-nxki)

Background
Enhertu 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 two or more prior anti-HER2-based regimens in the metastatic setting
- 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.

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, 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** in patients 18 years of age or older with unresectable or metastatic HER2-positive breast cancer or locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma and if the conditions indicated below are met.

Enhertu is considered **investigational** for patients less than 18 years of age and for all other indications.

Prior-Approval Requirements

Age 18 years of age or older

Diagnosis

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

1. Unresectable or metastatic HER2-positive breast cancer
    a. Patient has received two or more prior anti-HER2-based regimens in the metastatic setting
2. 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

Diagnosis

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

1. Unresectable or metastatic HER2-positive breast cancer
2. 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 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).

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 2021.

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

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 12, 2021 and is effective on April 1, 2021.