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Revised: 04/15/25

Subject: Fam-trastuzumab deruxtecan-nxki injection (Enhertu®)

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DESCRIPTION:

Fam-trastuzumab deruxtecan-nxki injection (Enhertu®) was approved by the U.S. Food and Drug Administration (FDA) in December 2019 for the treatment of 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. This indication was approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

Fam-trastuzumab deruxtecan is a HER2-targeted antibody-drug conjugate (ADC) that contains the humanized anti-HER2 IgG1, trastuzumab, covalently linked to the topoisomerase I inhibitor drug, DXd (a derivative of exatecan) by a stable protease-cleavable maleimide tetrapeptide linker. Fam-trastuzumab deruxtecan should not be substituted for or with other trastuzumab-based products.

The safety and efficacy of fam-trastuzumab deruxtecan were evaluated in a single-arm clinical trial (DESTINY-Breast01) of patients with HER2-positive, unresectable or metastatic breast cancer previously treated with two or more prior anti-HER2 therapies (N=184). Patients were excluded for a history of treated ILD or current ILD at screening. Patients were also excluded for history of clinically significant cardiac disease, active brain metastases, and ECOG performance status >1.

Fam-trastuzumab deruxtecan was administered as a 5.4 mg/kg infusion. Patients receiving fam-trastuzumab deruxtecan resulted in an objective response rate of 60.9% (95% CI, 53.4% to 68%) including a complete response in 6% at a median follow-up of 11.1 months**.** The median duration of response was 14.8 months (95% CI, 13.8 to 16.9 months) and median progression-free survival was 16.4 months (95% CI, 12.7 months to not reached). The disease control rate was 97.3% and the estimated

overall survival was 86.2% (95% CI, 79.8% to 90%) at 12 months; the median overall survival was not reached.

Patients had previously received a median of six (2-27) treatments including trastuzumab emtansine (100%), trastuzumab (100%), pertuzumab (65.8%) or other anti-HER2 therapy (54.3%). The median number of prior cancer regimens in the locally advanced/metastatic setting was 5 (range: 2-17). All patients received prior trastuzumab, ado-trastuzumab emtansine, and 66% had prior pertuzumab. Adverse events included interstitial lung disease in 13.6% of the patients, including Grade 3 events in 0.5% and resulting in death in 2.2%. No clinically significant cardiotoxicity was noted.

Fam-trastuzumab deruxtecan-nxki injection is included in NCCN guidelines for treatment of Breast Cancer (Version 1.2024), Central Nervous System Cancer (Version 1.2023), Cervical Cancer (Version 2.2024), Colon Cancer (Version 1.2024), Gastric Cancer (Version 3.2023), Head and Neck Cancer (Version 3.2024), Non-Small Cell Lung Cancer (Version 2.2024), Ovarian Cancer (Version 1.2024), Rectal Cancer (Version 1.2024), Uterine Neoplasms (Version 1.2024).

POSITION STATEMENT:

Initiation of fam-trastuzumab deruxtecan-nxki injection (Enhertu) **meets the definition of medical necessity** for members diagnosed with ANY of the following conditions when ALL associated criteria are met:

1. Ampullary Adenocarcinoma
    a. Member has disease progression
    b. Member has HER2-amplified disease
    c. Member has good performance status (ECOG 0-1)
    d. Dose does not exceed 5.4 mg/kg once every 3 weeks (21-day cycle)
2. Breast Cancer
    a. Member has recurrent unresectable (local or regional) or stage IV (M1) breast cancer or inflammatory breast cancer with no response to preoperative systemic therapy
    b. Member has HER2-low disease (IHC 0+, 1+, or 2+/ISH-) **OR** HER2-positive disease defined as **ONE** of the following:
        i. Immunohistochemistry (IHC) is 3+
        ii. Dual-probe ISH assay results:
            - HER2/CEP17 ratio ≥2.0 **AND** average HER2 copy number ≥ 4.0 signals/cell
        iii. Concurrent dual-probe ISH assay and IHC results:
            - HER2/CEP17 ratio ≥2.0 **AND** average HER2 copy number <4.0 signals/cell and concurrent IHC 3+
            - HER2/CEP17 ratio <2.0 **AND** average HER2 copy number ≥6.0 signals/cell and concurrent IHC 2+ or 3+
            - HER2/CEP17 ratio <2.0 **AND** average HER2 copy number ≥4.0 and <6.0

signals/cell and concurrent IHC 3+

c. One of the following:
    i. Use will be as second-line therapy
    ii. Member has had rapid progression of disease within 6 months of neoadjuvant or adjuvant therapy (12 months for pertuzumab-containing regimens)
d. Dose does not exceed 5.4 mg/kg once every 3 weeks (21-day cycle)

3. Central Nervous System Cancers
    a. Member has limited or extensive brain metastases
    b. Member has HER2-positive breast cancer defined as **ONE** of the following:
        i. Immunohistochemistry (IHC) is 3+
        ii. Dual-probe ISH assay results:
            - HER2/CEP17 ratio ≥2.0 **AND** average HER2 copy number ≥ 4.0 signals/cell
        iii. Concurrent dual-probe ISH assay and IHC results:
            - HER2/CEP17 ratio ≥2.0 **AND** average HER2 copy number <4.0 signals/cell and concurrent IHC 3+
            - HER2/CEP17 ratio <2.0 **AND** average HER2 copy number ≥6.0 signals/cell and concurrent IHC 2+ or 3+
            - HER2/CEP17 ratio <2.0 **AND** average HER2 copy number ≥4.0 and <6.0 signals/cell and concurrent IHC 3+
    c. Dose does not exceed 5.4 mg/kg once every 3 weeks (21-day cycle)
4. Cervical Cancer
    a. Member has local/regional recurrent disease **OR** stage IVB or recurrent disease with distant metastases
    b. Member has HER2-positive disease (IHC 3+ or 2+)
    c. Use will be as second-line or subsequent therapy
    d. Dose does not exceed 5.4 mg/kg once every 3 weeks (21-day cycle)
5. Colon Cancer
    a. Member has advanced, unresectable, inoperable, or metastatic disease
    b. Member has HER2-amplified disease
    c. Dose does not exceed 5.4 mg/kg once every 3 weeks (21-day cycle)
6. Endometrial Carcinoma
    a. Member has local/regional recurrent disease
    b. Member has HER2-positive disease (IHC 3+ or 2+)
    c. Use will be as second-line or subsequent therapy

d. Dose does not exceed 5.4 mg/kg once every 3 weeks (21-day cycle)

7. Esophageal and Esophagogastric Junction Cancers
    a. Member has HER2 overexpression positive disease
    b. Member is not a surgical candidate or has unresectable locally advanced, recurrent, or metastatic disease
    c. Use will be as second-line or subsequent therapy
    d. Dose does not exceed 5.4 mg/kg once every 3 weeks (21-day cycle)
8. Gastric Cancer
    a. Member has HER2 overexpression positive disease
    b. Member is not a surgical candidate or has unresectable locally advanced, recurrent, or metastatic disease
    c. Use will be as second-line or subsequent therapy
    d. Dose does not exceed 6.4 mg/kg once every 3 weeks (21-day cycle)
9. Non-small cell lung cancer
    a. Member has recurrent, advanced, or metastatic disease
    b. Member has ERBB2 (HER2) mutation positive disease
    c. Use will be as subsequent therapy
    d. Dose does not exceed 6.4 mg/kg once every 3 weeks (21-day cycle)
10. Ovarian Cancer (including fallopian tube cancer, primary peritoneal cancer, low-grade serous carcinoma, grade 1 endometrioid carcinoma, mucinous neoplasms of the ovary, clear cell carcinoma of the ovary, carcinosarcoma)
    a. Member has platinum-resistant persistent or recurrent disease
    b. Member has HER2-positive disease (IHC 3+ or 2+)
    c. Dose does not exceed 5.4 mg/kg once every 3 weeks (21-day cycle)
11. Rectal Cancer
    a. Member has advanced, unresectable, inoperable, or metastatic disease
    b. Member has HER2-amplified disease
    c. Dose does not exceed 5.4 mg/kg once every 3 weeks (21-day cycle)
12. Salivary Gland Tumors
    a. Member has recurrent disease
    b. Member has HER2-positive disease defined as **ONE** of the following:
        i. Immunohistochemistry (IHC) is 3+
        ii. Dual-probe ISH assay results:
            - HER2/CEP17 ratio ≥2.0 **AND** average HER2 copy number ≥ 4.0 signals/cell

iii. Concurrent dual-probe ISH assay and IHC results:

- HER2/CEP17 ratio ≥2.0 **AND** average HER2 copy number <4.0 signals/cell and concurrent IHC 3+
- HER2/CEP17 ratio <2.0 **AND** average HER2 copy number ≥6.0 signals/cell and concurrent IHC 2+ or 3+
- HER2/CEP17 ratio <2.0 **AND** average HER2 copy number ≥4.0 and <6.0 signals/cell and concurrent IHC 3+

c. Dose does not exceed 5.4 mg/kg once every 3 weeks (21-day cycle)

13. Other FDA-approved or NCCN supported diagnosis (not previously listed above)
    a. Member meets one of the following:
        i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) AND member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)
        ii. Indication AND usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation
    b. Dose does not exceed FDA label

Approval duration: 6 months

Continuation of fam-trastuzumab deruxtecan-nxki injection (Enhertu) **meets the definition of medical necessity** when all of the following criteria are met:

1. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for treatment of ampullary adenocarcinoma, breast cancer, colon cancer, gastric cancer, esophageal and esophagogastric junction cancers, salivary gland tumors, non-small cell lung cancer, rectal cancer, or other FDA-approved or NCCN supported diagnosis, **OR** the member has previously met all indication-specific initiation criteria
2. Member's disease has not progressed during treatment with fam-trastuzumab deruxtecan-nxki
3. Dose does not exceed FDA label

Approval duration: 6 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- 5.4 mg/kg given as an intravenous infusion over 35 to 60 minutes once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity
- Do not substitute for or with trastuzumab or ado-trastuzumab emtansine

- For intravenous infusion only

Dose Adjustments

- Management of adverse reactions (ILD, neutropenia, or left ventricular dysfunction) may require temporary interruption, dose reduction, or discontinuation of ENHERTU30 milligrams per kilogram of body weight once weekly

Drug Availability

- 100 mg lyophilized powder in a single-dose vial

PRECAUTIONS:

Boxed Warning

- Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported
- Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms
- Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis
- Advise patients of the risk and to immediately report symptoms

Contraindications

- None

Precautions/Warnings

- The most common adverse reactions (≥20%) were nausea, fatigue, vomiting, alopecia, constipation, decreased appetite, anemia, neutropenia, diarrhea, leukopenia, cough, and thrombocytopenia

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J9358	Injection, fam-trastuzumab deruxtecan-nxki, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

C06.9	Malignant neoplasm of mouth, unspecified
C07	Malignant neoplasm of parotid gland
C08.0 – C08.9	Malignant neoplasm of other and unspecified major salivary glands
C15.3 – C15.9	Malignant neoplasm of esophagus
C16.0 – C16.9	Malignant neoplasm of stomach
C18.0 – C18.9	Malignant neoplasm of colon
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum

C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C33	Malignant neoplasm of trachea
C34.00 – C34.92	Malignant neoplasm of bronchus and lung
C48.1 – C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C50.011 – C50.929	Malignant neoplasm of female and male breast
C53.0 – C53.9	Malignant neoplasm of cervix uteri
C54.0 – C54.9	Malignant neoplasm of corpus uteri
C56.1 – C56.9	Malignant neoplasm of ovary
C57.00 – C57.02	Malignant neoplasm of fallopian tube
C57.10 – C57.12	Malignant neoplasm of broad ligament
C57.20 – C57.22	Malignant neoplasm of round ligament
C57.3	Malignant neoplasm of parametrium
C57.4	Malignant neoplasm of uterine adnexa, unspecified
C57.7 – C57.9	Malignant neoplasm of other specified female genital organs
C78.00 – C78.02	Secondary malignant neoplasm of lung
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C79.31	Secondary malignant neoplasm of brain
D37.9	Neoplasm of uncertain behavior of digestive organ, unspecified

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

Adjuvant Treatment: Additional cancer treatment given after the primary treatment to lower the risk that the cancer will return. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biologic therapy. Adjuvant therapy can be used after or in combination

with another form of cancer therapy and is commonly used following removal of a cancerous tumor to further help in treatment.

Metastatic cancer: when cancer spreads from the primary site (place where it started) to other places in the body.

Neo-adjuvant treatment: Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy. It is a type of induction therapy.

RELATED GUIDELINES:

None.

OTHER:

None.

REFERENCES:

1. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2025 [cited 2/1/25]. Available from: http://www.clinicalpharmacology.com/.
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3. Daiichi Sankyo. Enhertu (fam-trastuzumab deruxtecan-nxki) injection. 2020 [cited 2/1/24]. In: DailyMed [Internet]. Bethesda (MD): National Library of Medicine. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7e67e73e-ddf4-4e4d-8b50-09d7514910b6/.
4. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2/1/25].
5. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2025 [cited 2/1/25]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 03/12/25.

GUIDELINE UPDATE INFORMATION:

03/15/20	New Medical Coverage Guideline.
07/01/20	Revision: Added HCPCS code J9358 and deleted code J9999.
09/15/21	Revision to position statement.
04/15/22	Review and revision to guideline; Updated position statement and references
05/15/22	Updated ICD10 codes.
07/15/22	Update to Billing and Coding Information Section.
09/15/22	Revision to position statement.
04/15/23	Review and revision; updated position statement, references.

04/15/24	Review and revision; updated position statement, coding, references.
04/15/25	Review and revision; updated position statement, coding, references.