Evolent Clinical Guideline 3035 for Enhertu™ (fam-trastuzumab deruxtecan-nxki)

Guideline Number:	Applicable Codes	
Evolent_CG_3035		
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STATEMENT

Purpose

To define and describe the accepted indications for Enhertu (fam-trastuzumab deruxtecan-nxki) usage in the treatment of cancer, including FDA approved indications, and off-label indications.

Evolent is responsible for processing all medication requests from network ordering providers. Medications not authorized by Evolent may be deemed as not approvable and therefore not reimbursable.

The use of this drug must be supported by one of the following: FDA approved product labeling, CMS-approved compendia, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) clinical guidelines, or peer-reviewed literature that meets the requirements of the CMS Medicare Benefit Policy Manual Chapter 15.

INDICATIONS

Continuation requests for a not-approvable medication shall be exempt from this Evolent policy provided

- The member has not experienced disease progression on the requested medication AND
- The requested medication was used within the last year without a lapse of more than 30 days of having an active authorization AND
- Additional medication(s) are not being added to the continuation request.

HER-2 Positive Breast Cancer

- Enhertu (fam-trastuzumab deruxtecan-nxki) may be used as monotherapy as neoadjuvant treatment in adult members with HER2-positive Stage II or III breast cancer, as determined by an FDA-authorized test followed by a taxane, trastuzumab/trastuzumab biosimilar, and pertuzumab/pertuzumab biosimilar (THP).
- Enhertu (fam-trastuzumab deruxtecan-nxki) may be used as monotherapy as adjuvant treatment in adult members with HER-2 positive breast cancer that has a high risk of recurrence following neoadjuvant therapy.
    - High risk of recurrence is defined as operable cancer (cT1-3, N0-1, M0) with axillary node-positive disease (ypN1-3) following neoadjuvant therapy

HER-2 Positive Metastatic/Recurrent Breast Cancer

- The member has recurrent or metastatic HER-2 positive breast cancer AND Enhertu (fam-trastuzumab deruxtecan-nxki) will be used as monotherapy for any of the following clinical settings:
    - As first-line therapy, for recurrent/metastatic disease, in a member who has

experienced disease progression within 6 months of neoadjuvant/adjuvant treatment or within 12 months of extended adjuvant treatment with an anti-HER2 containing regimen [e.g., Herceptin (trastuzumab)/trastuzumab biosimilar +/- Perjeta (pertuzumab)/pertuzumab biosimilar +/- chemotherapy].

- As second line/subsequent therapy in the metastatic setting.

- Enhertu (fam-trastuzumab deruxtecan-nxki) may be used in combination with pertuzumab/pertuzumab biosimilar as first-line treatment in adult members with unresectable or metastatic HER-2 positive (IHC 3+ or ISH+) breast cancer.

HER-2 LOW Metastatic Breast Cancer

- Enhertu may be used as a single agent in metastatic HER-2 LOW breast cancer. HER-2 LOW is defined as one of the following: HER-2 IHC staining 2+ with a negative ISH/FISH, or HER-2 by IHC of 1+ (in which case FISH/ISH is not required); the above definition is regardless of Hormone Receptor status. Member should have received one or more lines of systemic chemotherapy for metastatic breast cancer excluding hormonal agents [for example Faslodex (fulvestrant) or CDK 4/6 inhibitors [e.g., Ibrance (Palbociclib), Kisqali (ribociclib), Verzenio (abemaciclib)].

(HR)-Positive, HER-2 LOW or HER-2 ULTRALOW Metastatic Breast Cancer

- Enhertu (fam-trastuzumab deruxtecan-nxki) may be used as a single agent in adult members with hormone receptor (HR)-positive, HER-2 low (IHC 1+ or IHC 2+/ISH-) or HER-2 ultralow (IHC 0 with membrane staining) breast cancer that has progressed on one or more endocrine therapies in the metastatic setting.

HER-2 Positive, Metastatic/Recurrent Gastric, Esophageal and GE Junction Adenocarcinoma

- The member has metastatic/recurrent, HER-2 positive gastric, esophageal or GE Junction adenocarcinoma AND
- The member has experienced disease progression on a prior regimen that included trastuzumab/trastuzumab biosimilar AND
- Enhertu (fam-trastuzumab deruxtecan-nxki) will be used as a single agent.

Non-Small Cell Lung Cancer (NSCLC)

- The member has unresectable or metastatic non-small cell lung cancer with an activating ERBB-2/HER-2 mutation and Enhertu (fam-trastuzumab deruxtecan-nxki) may be used following at least one prior systemic therapy.

Solid Tumors

- Enhertu (fam-trastuzumab deruxtecan-nxki) may be used in adult members with unresectable or metastatic HER 2 positive (FISH+, or IHC 3+ or 2+) solid tumors who

have received prior systemic treatment and have no satisfactory alternative treatment options.

CONTRAINDICATIONS/WARNINGS

- US Boxed Warning
  - Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with fam-trastuzumab deruxtecan. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue fam-trastuzumab deruxtecan in all patients with ≥ grade 2 ILD/pneumonitis. Advise patients of the risk and the need to immediately report symptoms.
  - Exposure to fam-trastuzumab deruxtecan during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.

EXCLUSION CRITERIA

- Enhertu (fam-trastuzumab deruxtecan-nxki) is being used during or after disease progression with the same regimen.
- For HER-2 positive Gastric, Esophageal and GE Junction adenocarcinoma: Use of Enhertu (fam-trastuzumab deruxtecan-nxki) without receiving prior trastuzumab treatment.
- Dosing exceeds single dose limit of Enhertu (fam-trastuzumab deruxtecan-nxki) 5.4 mg/kg (for breast cancer, NSCLC, and solid tumors) and 6.4 mg/kg (for gastric, esophageal, or GE junction cancer).
- Investigational use of Enhertu (fam-trastuzumab deruxtecan-nxki) with an off-label indication that is not sufficient in evidence or is not generally accepted by the medical community. Sufficient evidence that is not supported by CMS recognized compendia or acceptable peer reviewed literature is defined as any of the following:
  - Whether the clinical characteristics of the patient and the cancer are adequately represented in the published evidence.
  - Whether the administered chemotherapy/biologic therapy/immune therapy/targeted therapy/other oncologic therapy regimen is adequately represented in the published evidence.
  - Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients. Generally, the definition of Clinically Meaningful outcomes are those recommended by ASCO, e.g., Hazard Ratio of less than 0.80 and the recommended survival benefit for OS and PFS should be at least 3 months.
  - Whether the experimental design, in light of the drugs and conditions under investigation, is appropriate to address the investigative question. (For example, in some clinical studies, it may be unnecessary or not feasible to use randomization,

double blind trials, placebos, or crossover).

- That non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs.
- That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.
- That abstracts (including meeting abstracts) without the full article from the approved peer-reviewed journals lack supporting clinical evidence for determining accepted uses of drugs.

CODING AND STANDARDS

Codes

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

Applicable Lines of Business

☐	CHIP (Children's Health Insurance Program)
☒	Commercial
☒	Exchange/Marketplace
☒	Medicaid
☐	Medicare Advantage

POLICY HISTORY

Date	Summary
July 2026	• Updated solid tumors indication
June 2026	• Updated indication section to include use as monotherapy as neoadjuvant therapy in adult members with HER2-positive Stage II or III breast cancer, followed by a taxane, trastuzumab/trastuzumab biosimilar, and pertuzumab/pertuzumab biosimilar (THP) • Updated references

Date	Summary
April 2026	• Updated indication section to include use as monotherapy as adjuvant treatment in adult members with HER-2 positive breast cancer that has a high risk of recurrence following neoadjuvant therapy • Updated references
January 2026	• Updated HER-2 positive metastatic/recurrent breast cancer indication section • Updated contraindications/warnings section • Updated references
March 2025	• Converted to new Evolent guideline template • This guideline replaces UM ONC_1379 Enhertu (fam-trastuzumab deruxtecan-nxki) • Added new indication • Updated exclusion criteria • Updated references
September 2024	• Removed “HER-2 overexpression” statement in exclusion criteria • Updated references
May 2024	• Added “solid tumors” to indication section • Added new references

LEGAL AND COMPLIANCE

Guideline Approval

Committee

Reviewed / Approved by Evolent Specialty Services Clinical Guideline Review Committee

Disclaimer

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