Fam-trastuzumab Deruxtecan-nxki (Enhertu®)

IMPORTANT REMINDER

We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the medical policy and a health plan or government program (e.g., TennCare), the express terms of the health plan or government program will govern.

POLICY

INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

HER2-Positive Metastatic Breast Cancer
Enhertu, as monotherapy, is indicated for the treatment of adult patients with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive [immunohistochemistry score (IHC) 3+ or in situ hybridization test (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.
Enhertu, in combination with pertuzumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH +) breast cancer as determined by an FDA-approved test.

HER2-Low and HER2-Ultralow Metastatic Breast Cancer
Enhertu is indicated 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-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.
- 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-approved test, that has progressed on one or more endocrine therapies in the metastatic setting.

HER2- Mutant Unresectable or Metastatic Non-Small Cell Lung Cancer (NSCLC)
Enhertu is indicated 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-approved test, and who have received a prior systemic therapy.

HER2-Positive Locally Advanced or Metastatic Gastric Cancer
Enhertu is indicated for the treatment of adult patients with locally advanced or metastatic HER2-positive (IHC 3+ or IHC 2+/ISH positive) gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

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

Enhertu is indicated 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.

Compendial Uses

- HER2-positive breast cancer, treatment of recurrent disease
- HER2-low and ultralow breast cancer, treatment of recurrent disease
- Non-small cell lung cancer with HER2 mutations, treatment of recurrent and advanced disease
- HER2-positive esophageal, gastric or gastroesophageal junction cancer
- HER2-positive solid tumors
  - HER2-amplified colorectal cancer (including appendiceal and anal adenocarcinoma)
  - HER2-positive cervical cancer
  - HER2-positive endometrial carcinoma
  - HER2-positive ovarian cancer
  - HER2-positive vaginal cancer
  - HER2-positive vulvar cancer
  - HER2-positive ampullary adenocarcinoma
  - HER2-positive salivary gland tumor
  - HER2-positive pancreatic adenocarcinoma
  - HER2-amplified small bowel adenocarcinoma
  - HER2-positive occult primary
  - HER2-positive appendiceal neoplasms and cancers
  - HER2-positive bladder cancer
  - HER2-positive biliary tract cancer
  - HER2-positive esophageal and esophagogastric adenocarcinoma
  - HER2-positive gastric adenocarcinoma

All other indications are considered experimental/investigational and not medically necessary.

DOCUMENTATION

Submission of the following information is necessary to initiate the prior authorization review: human epidermal growth factor receptor 2 (HER2) status (e.g., immunohistochemistry [IHC] score, in situ hybridization [ISH] test) and hormone receptor (HR) status.

COVERAGE CRITERIA

Breast cancer

Authorization of 12 months may be granted for treatment of breast cancer when any of the following criteria are met:

- Member has HER2-positive breast cancer and meets either of the following criteria:
  - The requested medication will be used as a single agent when the disease had no response to preoperative systemic therapy, or the disease is recurrent, metastatic, or unresectable.
  - The requested medication will be used in combination with pertuzumab as first line treatment when the disease had no response to preoperative systemic therapy, or the disease is unresectable or metastatic.
  - The requested medication will be used as adjuvant therapy for residual disease in members with high risk of recurrence (i.e., inoperable cancer at presentation prior to neoadjuvant therapy or operable cancer with axillary node-positive disease following preoperative therapy).

- Member has HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer and meets all of the following criteria:
  - The disease had no response to preoperative systemic therapy, or the disease is recurrent, metastatic, or unresectable.
  - The requested medication will be used as a single agent.
- Member has HER2-ultralow (IHC 0 with membrane staining) breast cancer and meets all of the following criteria:
  - The disease is recurrent, metastatic, or unresectable.
  - The disease is hormone receptor positive with visceral crisis or endocrine therapy refractory or the disease is hormone receptor negative.
  - The requested medication will be used as a single agent.
- Member has HER2-negative breast cancer and meets all of the following criteria:
  - The disease had no response to preoperative systemic therapy, or the disease is recurrent unresectable or metastatic.
  - The disease is hormone receptor positive with visceral crisis or endocrine therapy refractory.
  - The requested medication will be used as a single agent.

Non-Small Cell Lung Cancer

Authorization of 12 months may be granted for subsequent therapy of non-small cell lung cancer with HER2 (ERBB2) mutations or HER2 overexpression (IHC 3+) when all of the following criteria are met:

- The disease is recurrent, advanced, metastatic, or unresectable.
- The requested medication will be used as a single agent.
- The member has not experienced disease progression on a HER2 targeted drug (e.g., Kadycla).

Esophageal, Gastric or Gastroesophageal Junction Adenocarcinoma

Authorization of 12 months may be granted for members with HER2-positive disease who are not surgical candidates or for subsequent treatment of HER2-positive unresectable locally advanced, recurrent, or metastatic esophageal, gastric, or gastroesophageal junction adenocarcinoma as a single agent.

Solid Tumors

Authorization of 12 months may be granted for treatment of solid tumors when all of the following criteria are met:

- The disease is unresectable, metastatic, advanced, recurrent, or persistent.
- The tumor is HER2-positive (IHC 3+ or 2+).
- The member received prior systemic treatment and has no satisfactory alternative treatment options.
- The requested medication will be used as a single agent.

Biliary Tract Cancer

Authorization of 12 months may be granted for subsequent treatment of unresectable or resected gross residual (R2) disease or metastatic HER2-positive (IHC 3+) biliary tract cancer (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, or gallbladder cancer) when used as a single agent.

CONTINUATION OF THERAPY

Authorization of 12 months may be granted for continued treatment in members requesting reauthorization for an indication listed in the coverage criteria section when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

MEDICATION QUANTITY LIMITS

Drug Name	Diagnosis	Maximum Dosing Regimen
Enhertu (Fam-trastuzumab deruxtecan-nxki)	Ampullary Adenocarcinoma	Route of Administration: Intravenous 5.4mg/kg every 3 weeks
Enhertu (Fam-trastuzumab deruxtecan-nxki)	Biliary Tract Cancer	Route of Administration: Intravenous 5.4mg/kg every 3 weeks
Enhertu (Fam-trastuzumab deruxtecan-nxki)	Bladder cancer	Route of Administration: Intravenous 5.4mg/kg every 3 weeks
Enhertu (Fam-trastuzumab deruxtecan-nxki)	Breast Cancer	Route of Administration: Intravenous 5.4mg/kg every 3 weeks
Enhertu (Fam-trastuzumab deruxtecan-nxki)	Cervical Cancer	Route of Administration: Intravenous 5.4mg/kg every 3 weeks
Enhertu (Fam-trastuzumab deruxtecan-nxki)	Colorectal Cancer, including Appendiceal Adenocarcinoma and Anal Adenocarcinoma	Route of Administration: Intravenous 5.4mg/kg every 3 weeks
Enhertu (Fam-trastuzumab deruxtecan-nxki)	Endometrial Carcinoma	Route of Administration: Intravenous 5.4mg/kg every 3 weeks
Enhertu (Fam-trastuzumab deruxtecan-nxki)	Esophageal, Gastric or Gastroesophageal Junction Adenocarcinoma	Route of Administration: Intravenous 6.4mg/kg every 3 weeks
Enhertu (Fam-trastuzumab deruxtecan-nxki)	Non-Small Cell Lung Cancer (NSCLC)	Route of Administration: Intravenous 5.4mg/kg every 3 weeks
Enhertu (Fam-trastuzumab deruxtecan-nxki)	Occult Primary	Route of Administration: Intravenous 5.4mg/kg every 3 weeks
Enhertu (Fam-trastuzumab deruxtecan-nxki)	Ovarian, Fallopian, Primary Peritoneal Cancer	Route of Administration: Intravenous 5.4mg/kg every 3 weeks
Enhertu (Fam-trastuzumab deruxtecan-nxki)	Pancreatic Adenocarcinoma	Route of Administration: Intravenous 5.4mg/kg every 3 weeks
Enhertu (Fam-trastuzumab deruxtecan-nxki)	Salivary Gland Tumor	Route of Administration: Intravenous 6.4mg/kg every 3 weeks
Enhertu (Fam-trastuzumab deruxtecan-nxki)	Small Bowel Adenocarcinoma	Route of Administration: Intravenous 5.4mg/kg every 3 weeks
Enhertu (Fam-trastuzumab deruxtecan-nxki)	Solid Tumors	Route of Administration: Intravenous 5.4mg/kg every 3 weeks

Enhertu (Fam-trastuzumab deruxtecan-nxki)	Vaginal Cancer	Route of Administration: Intravenous 5.4mg/kg every 3 weeks
Enhertu (Fam-trastuzumab deruxtecan-nxki)	Vulvar Cancer	Route of Administration: Intravenous 5.4mg/kg every 3 weeks

APPLICABLE TENNESSEE STATE MANDATE REQUIREMENTS

BlueCross BlueShield of Tennessee's Medical Policy complies with Tennessee Code Annotated Section 56-7-2352 regarding coverage of off-label indications of Food and Drug Administration (FDA) approved drugs when the off-label use is recognized in one of the statutorily recognized standard reference compendia or in the published peer-reviewed medical literature.

ADDITIONAL INFORMATION

For appropriate chemotherapy regimens, dosage information, contraindications, precautions, warnings, and monitoring information, please refer to one of the standard reference compendia (e.g., the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) published by the National Comprehensive Cancer Network®, Drugdex Evaluations of Micromedex Solutions at Truven Health, or The American Hospital Formulary Service Drug Information).

REFERENCES

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3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Anal Carcinoma. Version 4.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf. Accessed September 3, 2025.
4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 4.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed September 3, 2025.
5. National Comprehensive Cancer Network .NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers. Version 5.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed September 3, 2025.

EFFECTIVE DATE 6/30/2026

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