Enhertu
(fam-trastuzumab deruxtecan-nxki)

Override(s)	Approval Duration
Prior Authorization	1 year

Medications
Enhertu (fam-trastuzumab deruxtecan-nxki)

APPROVAL CRITERIA

Requests for Enhertu (fam-trastuzumab deruxtecan-nxki) may be approved if the following criteria are met:

I. Individual has a diagnosis of recurrent unresectable or metastatic HER2-positive (HER2+) breast cancer (Label, NCCN 1) and meets *one* of the following HER2 levels:
   A. Immunohistochemistry (IHC) is 3 +; **OR**
   B. In situ hybridization (ISH) positive;
   AND

II. Individual has previously received a prior anti-HER2 therapy in either:
   A. Metastatic setting; **OR**
   B. In the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy;

OR

III. Individual has a diagnosis of unresectable or metastatic HER2-Low breast cancer and meets one of the following HER2 levels (Label, NCCN 1, 2A):
   A. IHC is 1+; **OR**
   B. IHC is 2+/ISH negative;
   AND

IV. Individual is using as a single agent; **AND**

V. Individual is using in one of the following ways:
   A. Individual has progressed on one or more endocrine therapies in the metastatic setting; **OR**
   B. Individual has prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy;

OR

VI. Individual has a diagnosis of unresectable or metastatic HER2-Ultralow breast cancer (Label); **AND**
   A. Individual has IHC 0 with member straining; **AND**
   B. Individual is using as a single agent; **AND**

C. Individual has progressed on one or more endocrine therapies in the metastatic setting;

OR

VII. Individual has a diagnosis of HER2-positive cervical cancer, including vaginal cancer (NCCN 2A); **AND**

A. Individual meets one of the following HER2 levels:
    1. IHC 3+ ; **OR**
    2. IHC 2+;

AND

B. Individual is using as second-line or subsequent therapy; **AND**
C. Individual is using as a single agent; **AND**
D. Using in one of the following disease states:
    1. Local/regional recurrence; **OR**
    2. Stage IVB or recurrence with distant metastases;

OR

VIII. Individual has a diagnosis of colorectal cancer (including appendiceal adenocarcinoma) (NCCN 2A); **AND**

A. Individual is using as initial treatment; **AND**
    1. Individual is using as a single agent; **AND**
    2. Individual has HER2-amplified (defined as IHC 3+ or ISH positive) and RAS and BRAF wild-type disease; **AND**
    3. Individual has unresectable metachronous metastases pMMR/MSS only and previous FOLFOX or CapeOX treatment within the past 12 months;

OR

B. Individual is using as subsequent therapy; **AND**
    1. Individual is using as a single agent; **AND**
    2. Using in one of the following disease states:
        a. Individual has advanced disease; **OR**
        b. Individual has metastatic disease which is proficient mismatch repair/microsatellite-stable (pMMR/MSS) or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) or polymerase epsilon/delta [POLE/POLD1] mutation who are HER2-amplified (defined as IHC 3+ or ISH positive) and RAS and BRAF wild-type; **OR**
        c. Adjuvant treatment for unresectable metachronous metastases that converted to resectable disease after initial treatment;

OR

IX. Individual has a diagnosis of HER2-Positive disease in **solid tumors** (Label, NCCN 2A); **AND**

A. Individual has HER2 levels of IHC 3+; **AND**
B. Individual has an unresectable or metastatic solid tumor; **AND**
C. Individual has had prior systemic treatment; **AND**

D. Individual has no satisfactory alternative treatment options; **AND**
E. Individual is using as a single agent;

OR

X. Individual has a diagnosis of unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations and who have received a prior systemic therapy (Label, NCCN 2A));

OR

XI. Individual has a diagnosis of locally advanced or metastatic HER2+ gastric or esophageal and esophagogastric junction cancers and meets *one* of the following HER2 levels (Label, NCCN 2A):
A. IHC 3 +; **OR**
B. IHC2+/ISH positive;
AND

XII. Individual has received a prior trastuzumab (or trastuzumab biosimilars)-based regimen;

OR

XIII. Individual has a diagnosis of HER2-positive endometrial carcinoma (NCCN 2A); **AND**
A. Individual meets one of the following HER2 levels:
1. IHC 3+; **OR**
2. IHC 2+;

AND

B. Individual is using as second-line or subsequent therapy; **AND**
C. Individual is using for recurrent disease;

OR

XIV. Individual has a diagnosis of metastatic HER2 + breast cancer with brain metastases and the following criteria are met (NCCN 2A):
A. Individual has a primary diagnosis of HER2+ breast cancer; **AND**
B. Using in one of the following ways:
1. In those with asymptomatic brain metastases as primary or initial therapy; **OR**
2. In those with stable brain metastases disease in relapsed/recurrent disease;

AND

C. Individual is using as a single-agent treatment.

Requests for Enhertu (fam-trastuzumab deruxtecan-nxki) may not be approved for the following:

I. When Enhertu is used in combination with other targeted biologic agents or chemotherapy agents; **OR**
II. Individual has a history of Interstitial Lung Disease (ILD)/pneumonitis requiring treatment with steroids or ongoing ILD/pneumonitis; **OR**
III. When the above criteria are not met and for all other indications.

NOTE:
Enhertu has a black box warning for interstitial lung disease and embryo-fetal toxicity. Interstitial lung disease (ILD) and pneumonitis, including fata cases, have been reported with Enhertu. Patients should be monitored for signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Enhertu should be discontinued in all patients with Grade 2 or higher ILD/pneumonitis.

Key References:

1. Cortés J, Kim S-B, Chung W-P, et al. Trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1) in patients with HER2+ metastatic breast cancer: results of the randomized, phase 3 study DESTINY-Breast03. ESMO 2021
2. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Updated periodically.
3. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
4. Jerusalem G, Park YH, Yamashita T, et al. Trastuzumab deruxtecan (T-DXd) in patients with HER2+ metastatic breast cancer with brain metastases: a subgroup analysis of the DESTINY-Breast01 trial. ASCO 2021
5. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2025; Updated periodically.
6. Li BT, et al. Trastuzumab deruxtecan in HER2-mutant non-small-cell lung cancer. N Engl J Med 2022;386:241-251.
7. Modi S, Saura C, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive breast Cancer. N Eng J Med 2019: 10.1056/NEJMoa1914510.
8. NCCN Clinical Practice Guidelines in Oncology™. © 2025 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on January 17, 2025.
    a. Breast Cancer. V6.2024. Revised November 11, 2024.
    b. Central Nervous System Cancers V3.2024. Revised September 30, 2024.
    c. Cervical Cancer. V1.2025. Revised December 19, 2024.
    d. Colon Cancer V6.2024. Revised January 17, 2025.
    e. Esophageal and esophagogastric junction cancers. V5.2024. Revised December 20, 2024.
    f. Gastric Cancer. V2.2023. Revised August 29, 2023.
    g. Head and neck cancers. V1.2025. Revised November 26, 2024
    h. Non-Small Cell Lung Cancer. V3.2025. Revised January 14, 2025.
    i. Rectal Cancer V4.2024. Revised August 22, 2024.
    j. Uterine neoplasms. V1.2025. Revised December 16, 2024.
9. Siena S, Di Bartolomeo M, Raghav K, et al. Trastuzumab deruxtecan (DS-8201) in patients with HER2-expressing metastatic colorectal cancer (DESTINY-CRC01): a multicentre, open-label, phase 2 trial. Lancet Oncol 2021;22:779-789.
10. Smit EF, Nakagawa K, Nagasaka M, et.al. Trastuzumab deruxtecan in patients with HER2-mutated metastatic non-small cell lung cancer; interim results of DESTINY-Lung01[abstract]. J Clin Oncol 2020;38;Abstract 9504.
11. Curigliano G, et al. Trastuzumab deruxtecan (T-DXd) vs. physician's choice of chemotherapy (TPC) in patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-low or HER2-ultralow metastatic breast cancer (mBC) with prior endocrine therapy (ET): Primary results from DESTINY-Breast06 (DB-06). J Clin Oncol 42(suppl 17): LBA1000. doi: 10.1200/JCO.2024.42.17_suppl.LBA1000

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.