Medical Policy:

Enhertu® (fam-trastuzumab deruxtecan-nxki) Intravenous

POLICY NUMBER	LAST REVIEW	ORIGIN DATE
MG.MM.PH.210	April 4, 2025	April 6, 2020

Definitions

Fam-trastuzumab deruxtecan-nxki is a HER2-directed antibody-drug 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, fam-trastuzumab deruxtecan-nxki undergoes internalization and intracellular linker cleavage by lysosomal enzymes. Upon release, the membrane-permeable DXd causes DNA damage and apoptotic cell death.

Length of Authorization

Coverage will be provided for 6 months and may be renewed.

Dosing Limits [Medical Benefit]

Max Units (per dose and over time):

5.4mg/kg/every 3 weeks (21-day cycle)

Max Units (per dose and over time) [HCPCS Unit]:

- Breast Cancer, NSCLC: 600 Billable Units Every 21 Days

- All Other Indications: 700 Billable Units Every 21 Days

Guideline

I. Initial Approval Criteria

Enhertu may be considered medically necessary if the below conditions are met AND use is consistent with the medical necessity criteria that follows:

1. Baseline left ventricular ejection fraction (LVEF) within normal limits; **AND**

1. Breast Cancer – HER2-Positive Disease.

A. Patient is ≥ 18 years of age; **AND**
B. Patient has recurrent or metastatic breast cancer; **AND**
C. Patient has human epidermal growth factor receptor 2 (HER2)-positive disease (immunohistochemistry [IHC] 3+ or in situ hybridization [ISH] positive); **OR**
D. Patient meets ONE of the following (i or ii):
   i. Patient has tried at least one prior regimen in the metastatic setting; **OR**
   ii. Patient has had disease recurrence during or within 6 months of completing neoadjuvant or adjuvant therapy (within 12 months for Perjeta [pertuzumab injection]-containing regimens) and the medication is used as first-line therapy; **AND**
E. The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 5.4 mg per kg administered as an intravenous infusion not more frequently than once every 3 weeks.

2. Breast Cancer – Hormone Receptor-Positive, HER2-Low or Ultra-Low Disease

A. Patient is ≥ 18 years of age; **AND**
B. Patient has recurrent, unresectable, or metastatic disease; **AND**
C. Patient has hormone receptor (HR) positive disease with visceral crisis or is refractory to endocrine therapy; **AND**
   Note: Visceral crisis is defined as severe organ dysfunction, as assessed by signs and symptoms, laboratory studies, and rapid disease progression.
D. Patient has human epidermal growth factor receptor 2 (HER2)-low or HER2-ultra-low disease as shown by immunohistochemistry [IHC] 0+, 1+, 2+ or in situ hybridization [ISH] negative; **AND**
E. Patient meets ONE of the following (i **OR** ii):
   i. The medication will be used as first-line therapy and meets BOTH of the following (a **AND** b):
      1. The disease is negative for germline *BRCA* 1/2 mutation; **AND**
      2. Patient has tried at least one line of endocrine-based therapy in the metastatic setting; **OR**
   ii. The medication will be used as second-line therapy; **AND**
F. The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 5.4 mg per kg administered as an intravenous infusion not more frequently than once every 3 weeks.

3. Breast Cancer – Hormone Receptor-Negative, HER2-Low or Ultra-Low Disease.

A. Patient is ≥ 18 years of age; **AND**
B. Patient has recurrent, unresectable, or metastatic disease; **AND**
C. Patient has hormone receptor (HR)-negative disease; **AND**
D. The disease is negative for germline *BRCA* 1/2 mutation; **AND**
E. Patient has human epidermal growth factor receptor 2 (HER2)-low or HER2-ultra-low disease as shown by immunohistochemistry [IHC] 0+, 1+, 2+ or in situ hybridization [ISH] negative; **AND**

F. Patient meets ONE of the following (i **OR** ii):
   i. The medication is considered for first-line therapy after the disease has progressed during or within 6 months after completing adjuvant chemotherapy; **OR**
   ii. The medication is used in the subsequent therapy setting (second- or later-line).
G. The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 5.4 mg per kg administered as an intravenous infusion not more frequently than once every 3 weeks.

4. Gastric or Gastroesophageal Junction Cancer.

A. Patient is ≥ 18 years of age; **AND**
B. Patient has human epidermal growth factor receptor 2 (HER2)-positive disease (immunohistochemistry [IHC] 3+ or IHC 2+/in situ hybridization [ISH] positive); **AND**
C. Patient has received at least one prior trastuzumab-based regimen; **AND**
D. The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 6.4 mg per kg administered as an intravenous infusion not more frequently than once every 3 weeks.

5. Non-Small Cell Lung Cancer.

A. Patient is ≥ 18 years of age; **AND**
B. Patient has unresectable or metastatic disease; **AND**
C. The disease has activating human epidermal growth factor receptor 2 (HER2) mutations; **AND**
D. Patient has tried at least one prior systemic therapy; **AND**
E. The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 5.4 mg per kg administered as an intravenous infusion not more frequently than once every 3 weeks.

6. Solid Tumors

Note: Examples include bladder cancer, biliary tract cancer, cervical cancer, colorectal cancer, endometrial cancer, ovarian cancer, pancreatic cancer, salivary gland tumors.

A. Patient is ≥ 18 years of age; **AND**
B. Patient has unresectable or metastatic disease; **AND**
C. Patient has human epidermal growth factor receptor 2 (HER2)-positive disease (immunohistochemistry [IHC] 3+); **AND**
D. Patient has received prior systemic treatment; **AND**
E. According to the prescriber, there are no satisfactory alternative treatment options; **AND**
F. The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 5.4 mg per kg administered as an intravenous infusion not more frequently than once every 3 weeks.

II. Renewal Criteria

Coverage can be renewed based upon the following criteria:

1. Patient continues to meet initial approval criteria; **AND**
2. Tumor response with stabilization of disease or decrease in size of tumor or tumor spread; **AND**
3. Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: cardiotoxicity (i.e. left ventricular dysfunction, cardiomyopathy); pulmonary toxicity (i.e. pneumonitis); neutropenia; infusion-related reactions; etc.; **AND**
4. Left ventricular ejection fraction (LVEF) has not had an absolute decrease of more than 20% from baseline and is within normal limits

Applicable Procedure Codes

Code	Description
J9358	Injection, fam-trastuzumab deruxtecan-nxki, 1 mg (Enhertu)

Applicable NDCs

Code	Description
65597-0406-01	Enhertu 100 mg single-dose vial

ICD-10 Diagnoses

Code	Description
C16.0	Malignant neoplasm of cardia
C16.1	Malignant neoplasm of fundus of stomach
C16.2	Malignant neoplasm of body of stomach
C16.3	Malignant neoplasm of pyloric antrum
C16.4	Malignant neoplasm of pylorus
C16.5	Malignant neoplasm of lesser curvature of stomach, unspecified
C16.6	Malignant neoplasm of greater curvature of stomach, unspecified
C16.8	Malignant neoplasm of overlapping sites of stomach
C16.9	Malignant neoplasm of stomach, unspecified
C33	Malignant neoplasm of trachea
C34.00	Malignant neoplasm of unspecified main bronchus
C34.01	Malignant neoplasm of right main bronchus
C34.02	Malignant neoplasm of left main bronchus
C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung

C43.52	Malignant melanoma of skin of breast
C44.501	Unspecified malignant neoplasm of skin of breast
C44.511	Basal cell carcinoma of skin of breast
C44.521	Squamous cell carcinoma of skin of breast
C44.591	Other specified malignant neoplasm of skin of breast
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.019	Malignant neoplasm of nipple and areola, unspecified female breast
C50.021	Malignant neoplasm of nipple and areola, right male breast
C50.022	Malignant neoplasm of nipple and areola, left male breast
C50.029	Malignant neoplasm of nipple and areola, unspecified male breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.119	Malignant neoplasm of central portion of unspecified female breast
C50.121	Malignant neoplasm of central portion of right male breast
C50.122	Malignant neoplasm of central portion of left male breast
C50.129	Malignant neoplasm of central portion of unspecified male breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.219	Malignant neoplasm of upper-inner quadrant of unspecified female breast
C50.221	Malignant neoplasm of upper-inner quadrant of right male breast
C50.222	Malignant neoplasm of upper-inner quadrant of left male breast
C50.229	Malignant neoplasm of upper-inner quadrant of unspecified male breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.319	Malignant neoplasm of lower-inner quadrant of unspecified female breast
C50.321	Malignant neoplasm of lower-inner quadrant of right male breast
C50.322	Malignant neoplasm of lower-inner quadrant of left male breast
C50.329	Malignant neoplasm of lower-inner quadrant of unspecified male breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.419	Malignant neoplasm of upper-outer quadrant of unspecified female breast
C50.421	Malignant neoplasm of upper-outer quadrant of right male breast
C50.422	Malignant neoplasm of upper-outer quadrant of left male breast
C50.429	Malignant neoplasm of upper-outer quadrant of unspecified male breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast

C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.519	Malignant neoplasm of lower-outer quadrant of unspecified female breast
C50.521	Malignant neoplasm of lower-outer quadrant of right male breast
C50.522	Malignant neoplasm of lower-outer quadrant of left male breast
C50.529	Malignant neoplasm of lower-outer quadrant of unspecified male breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.619	Malignant neoplasm of axillary tail of unspecified female breast
C50.621	Malignant neoplasm of axillary tail of right male breast
C50.622	Malignant neoplasm of axillary tail of left male breast
C50.629	Malignant neoplasm of axillary tail of unspecified male breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.819	Malignant neoplasm of overlapping sites of unspecified female breast
C50.821	Malignant neoplasm of overlapping sites of right male breast
C50.822	Malignant neoplasm of overlapping sites of left male breast
C50.829	Malignant neoplasm of overlapping sites of unspecified male breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.919	Malignant neoplasm of unspecified site of unspecified female breast
C50.921	Malignant neoplasm of unspecified site of right male breast
C50.922	Malignant neoplasm of unspecified site of left male breast
C50.929	Malignant neoplasm of unspecified site of unspecified male breast
Z85.3	Personal history of malignant neoplasm of breast
Z85.028	Personal history of other malignant neoplasm of stomach
Z85.118	Personal history of other malignant neoplasm of bronchus and lung

Revision History

Company(ies)	DATE	REVISION
EmblemHealth & ConnectiCare	4/4/2025	Annual Review: Breast Cancer – HER2-Positive Disease. Added qualifier “HER2-positive disease” to indication. Deleted criteria for HER2-low disease since it is now addressed separately. Breast Cancer – Hormone Receptor-Positive, HER2-Low or Ultra-Low Disease. Added new approval condition and criteria for HER2 ultra-low disease. Separated criteria for HER2-low disease from “HER2-Positive Disease” indication above. Breast Cancer – Hormone Receptor-Negative, HER2-Low or Ultra-Low Disease. Added new approval condition and criteria for HER2 ultra-low disease. Separated criteria for HR negative, HER2-low disease from “HER2-Positive Disease” indication above. Solid Tumors: Added new FDA-approved indication and approval criteria.

<table>
<tr><td></td><td></td><td>Updated diagnosis codes</td></tr>
<tr><td>EmblemHealth & ConnectiCare</td><td>3/18/2024</td><td>Annual Review: No criteria changes</td></tr>
<tr><td>EmblemHealth & ConnectiCare</td><td>07/06/2023</td><td>Annual Review:
<u>Initial Approval Criteria</u>: Removed “3. Patient’s cancer is human epidermal growth factor receptor 2 (HER2)-positive” and moved it under Breast Cancer.
<u>Breast Cancer</u>: Initial Criteria Removed “Patient has received 2 or more prior anti-HER2-based regimens in the metastatic setting.”
Added “Patient’s cancer is human epidermal growth factor receptor 2 (HER2)-positive; AND
Patient has received a prior anti-HER2-based regimen either:
i. in the metastatic setting; OR
ii. in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy.”
Added: HER2-Low Metastatic Breast Cancer Indication, Unresectable or Metastatic HER2-Mutant Non-Small Cell Lung Cancer Indication and Locally Advanced or Metastatic Gastric Cancer Indication
Updated dosing chart
Added Codes:
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<tr><td>C78.00</td><td>Secondary malignant neoplasm of unspecified lung</td></tr>
<tr><td>C78.01</td><td>Secondary malignant neoplasm of right lung</td></tr>
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		C78.02	Secondary malignant neoplasm of left lung	
		Z85.028	Personal history of other malignant neoplasm of stomach	
		Z85.118	Personal history of other malignant neoplasm of bronchus and lung	
EmblemHealth & ConnectiCare	04/21/2022	Transferred policy to new template		
EmblemHealth & ConnectiCare	06/11/2020	Added J-Code (J9358) Injection, fam-trastuzumab deruxtecan-nxki, 1 mg (Enhertu). Effective Date: 07/01/2020		
EmblemHealth & ConnectiCare	04/06/2020	New Medical Policy		

References

1. Product Information: ENHERTU® intravenous injection, fam-trastuzumab deruxtecan-nxki intravenous injection. Daiichi Sankyo Inc (per FDA), Basking Ridge, NJ, 2019.
2. NIOSH: The National Institute for Occupational Safety and Health (NIOSH): NIOSH list of antineoplastic and other hazardous drugs in healthcare settings, 2016. National Institute for Occupational Safety and Health (NIOSH). Cincinnati, OH. 2020. Available from URL: https://www.cdc.g... . As accessed 2020-03-20.
3. Centers for Disease Control and Prevention (CDC): NIOSH list of antineoplastic and other hazardous drugs in healthcare settings, 2016. Centers for Disease Control and Prevention (CDC). Atlanta, GA. 2016. Available from URL: http://www.cdc.go... . As accessed 2016-11-03.