STATE OF IOWA DEPARTMENT OF
Health AND Human
SERVICES

Enhertu (fam-trastuzumab deruxtecan-nxki)
PAM-018

Iowa Medicaid Program:	Prior Authorization	**Effective Date:**	01/01/2021
Revision Number:	4	**Last Rev Date:**	01/19/2024
Reviewed By:	Medicaid Medical Director	**Next Rev Date:**	01/17/2025
Approved By:	Medicaid Clinical Advisory Committee	**Approved Date:**	04/16/2021

Overview

Medication: [1]	fam-trastuzumab deruxtecan-nxki
Brand Name:	Enhertu®
Pharmacologic Category:	HER2-directed antibody and topoisomerase inhibitor conjugate
FDA-Approved Indication(s):	Treatment of adult patients with: 1. Unresectable or metastatic HER2-positive 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. 2. Unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. 3. 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. ➢ This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. 4. Locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.
How Supplied:	Single-dose vial: lyophilized powder, 100 mg
Dosage and Administration:	Intravenous (IV) infusion. Administer until disease progression or unacceptable toxicity. • Breast Cancer, NSCLC: 5.4 mg/kg once every 3 weeks (21-day cycle) • Gastric Cancer: 6.4 mg/kg once every 3 weeks (21-day cycle)
Benefit Category:	Medical

BOXED WARNING: : INTERSTITIAL LUNG DISEASE AND EMBRYO-FETAL TOXICITY

- Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with Enhertu®. 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.
- Exposure to Enhertu® during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.

Patient Selection (Biomarkers and Testing)	
Indication	Select patients for treatment with Enhertu® based on:
1. Unresectable or metastatic HER2-positive breast cancer	HER2 expression
2. Unresectable or Metastatic HER2-Low Breast Cancer	HER2 expression (IHC 1+ or IHC 2+/ISH-)
3. Unresectable or Metastatic HER2-Mutant NSCLC	The presence of activating *HER2 (ERBB2)* mutations in tumor or plasma specimens. If no mutation is detected in a plasma specimen, test tumor tissue.
4. Locally Advanced or Metastatic Gastric Cancer	HER2 protein overexpression or HER2 gene amplification. Reassess HER2 status if it is feasible to obtain a new tumor specimen after prior trastuzumab-based therapy and before treatment with Enhertu.
▪ American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) recommend that all newly diagnosed patients with breast cancer must have an HER2 test performed. Patients who then develop metastatic disease must have an HER2 test performed in a metastatic site, if tissue sample is available.[2] ▪ Information on FDA-approved tests for the detection of HER2 protein expression, HER2 gene amplification, and activating HER2 mutations is available at: www.fda.gov/CompanionDiagnostics.	

Descriptive Narrative

Breast cancer is a heterogenous, phenotypically diverse disease composed of several biologic subtypes that have distinct behavior. Amplification or overexpression of the human epidermal growth factor receptor 2 *(HER2)* oncogene* is present in approximately 15 percent of primary invasive breast cancers. Women with both early-stage and metastatic** breast cancer that meet criteria for HER2 positivity are treated with regimens including HER2-directed therapy.[3]

Globally, breast cancer is the most frequently diagnosed malignancy, accounting for over two million cases each year. In the United States, breast cancer is the most common female cancer, and the second most common cause of cancer death in women.[4] An estimated 2,770 new cases of breast cancer in females will be diagnosed in Iowa in 2022, making it the most commonly diagnosed cancer in the state, and with an estimated 380 deaths, it is the fifth highest cause of cancer deaths in Iowa in 2022.[5]

Up to 5 percent of women diagnosed with breast cancer in the U.S. have metastatic disease at the time of first presentation, despite the gains in early detection, and up to 30 percent of women with early-stage non-metastatic breast cancer at diagnosis will develop distant metastatic disease.

Lung cancer is the leading cause of cancer death in the United States. In 2023, an estimated 238,340 new cases (117,550 in males and 120,790 in females) of lung and bronchial cancer will be diagnosed, and 127,070 deaths (67,160 in males and 59,910 in females) are estimated to occur because of the disease. During the COVID pandemic, the diagnosis and treatment of lung cancer have been hampered; however, this has not been reflected in the 2023 estimates for incidence and mortality because of the typical delays in collecting and reporting the data. Only 22.9% of all patients with lung cancer are alive 5 years or more after diagnosis; this includes patients with non-small cell lung cancer (NSCLC) and those with small cell lung cancer (SCLC).

Much progress has been made recently for lung cancer, such as screening; minimally invasive techniques for diagnosis and treatment; advances in radiation therapy (RT), including stereotactic ablative radiotherapy (SABR); new targeted therapies; and new immunotherapies. These new treatments are reflected in the improved survival rates for patients with NSCLC. Patients with NSCLC who are eligible for targeted therapies or immunotherapies are now surviving longer; 5-year survival rates range from 15% to 50%, depending on the biomarker. Thus, death rates for lung cancer have been declining, although there are still more deaths from lung cancer than from breast, prostate, colorectal, and brain cancers combined.[6]

* HER2 is a growth-promoting protein on the outside of all breast cells. Breast cancer cells with higher-than-normal levels of HER2 are referred to as HER2-positive.

** Metastatic breast cancer (MBC). Also called stage IV, MBC is breast cancer that has spread to another part of the body, most commonly the liver, brain, bones, or lungs.

Guidelines

As new and emerging therapies are rapidly coming to market, oncology treatment recommendations and guidelines are constantly changing. To keep up with these changes, the National Comprehensive Cancer Network (NCCN) publishes guidelines which are developed and updated by 60 individual panels, comprising over 1,660 clinicians and oncology researchers from the 31 NCCN Member Institutions.[7]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a work in progress that may be refined as often as new significant data becomes available. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

The information referenced at the time of this policy writing/revision is from:

- NCCN Guidelines for Breast Cancer (Version 4.2023 – March 23, 2023)[8]
- NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers (Version 3.2023 – August 29, 2023)[9]
- NCCN Guidelines for Gastric Cancer (Version 2.2023 – August 29, 2023)[10]
- NCCN Guidelines for Non-Small Cell Lung Cancer (Version 5.2023 – November 8, 2023)[11]

NCCN Guidelines® Recommendation(s) for fam-trastuzumab deruxtecan-nxki – Breast Cancer [recurrent unresectable (local or regional) or stage IV (M1) disease]
(1) HR-Positive and HER2-Negative with Visceral Crisis [a] or Endocrine Refractory
A. HER2 IHC 1+ or 2+/ISH negative [b]
i. Category 1, preferred second-line therapy
(2) HR-Negative and HER2-Negative (Triple-Negative Breast Cancer, TNBC)
A. No germline *BRCA1/2* mutation [c] and HER2 IHC 1+ or 2+/ISH negative
i. Category 1, preferred second-line therapy [b]
(3) HR-Positive or -Negative and HER2-positive [d]
A. Category 1, preferred second-line therapy [e]

NCCN Guidelines® Recommendation(s) for fam-trastuzumab deruxtecan-nxki – Esophageal and Esophagogastric Junction Cancers [unresectable locally advanced, recurrent, or metastatic disease (where local therapy is not indicated)]
(1) Adenocarcinoma – HER2 overexpression positive A. Second-line or subsequent therapy (dependent on prior therapy and PS) i. Category 2A, preferred regimen

NCCN Guidelines® Recommendation(s) for fam-trastuzumab deruxtecan-nxki – Gastric Cancer [unresectable locally advanced, recurrent, or metastatic disease (where local therapy is not indicated)]
(1) Adenocarcinoma – HER2 overexpression positive A. Second-line or subsequent therapy (dependent on prior therapy and PS) i. Category 2A, preferred regimen

NCCN Guidelines® Recommendation(s) for fam-trastuzumab deruxtecan-nxki – Non-Small Cell Lung Cancer
(1) *ERBB2 (HER2)* mutation A. Category 2A, subsequent therapy

[a] According to the 5th ESO-ESMO international consensus guidelines (Cardoso F, et al. Ann Oncol 2020;31:1625) for advanced breast cancer visceral crisis is defined as: "severe organ dysfunction, as assessed by signs and symptoms, laboratory studies and rapid progression of disease. Visceral crisis is not the mere presence of visceral metastases but implies important organ compromise leading to a clinical indication for the most rapidly efficacious therapy."

[b] Fam-trastuzumab deruxtecan-nxki may be considered in a later line for HER2 IHC 1+ or 2+/ISH negative, if not used in second–line. Fam-trastuzumab deruxtecan-nxki is associated with interstitial lung disease (ILD)/pneumonitis. Regular monitoring for this serious side effect is recommended. For patients with a history of ILD/pneumonitis, there are no data on managing safety or toxicity of this drug in a trial.

[c] Assess for germline BRCA1/2 mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy.

[d] Assess for germline *BRCA1/2* mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy. While olaparib and talazoparib are FDA-indicated in HER2-negative disease, the panel supports use in any breast cancer subtype associated with a germline mutation. There is lower-level evidence for HER2-positive tumors, therefore category 2A for this setting.

[e] Fam-trastuzumab deruxtecan-nxki may be considered in the first-line setting as an option for select patients (i.e., those with rapid progression within 6 months of neoadjuvant or adjuvant therapy [12 months for pertuzumab-containing regimens]). Fam-trastuzumab deruxtecan-nxki is associated with interstitial lung disease (ILD)/pneumonitis. Regular monitoring for this serious side effect is recommended. For patients with a history of ILD/pneumonitis, there are no data on managing safety or toxicity of this drug in a trial.

NCCN Categories of Evidence and Consensus (all recommendations are category 2A unless otherwise indicated)	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

NCCN Categories of Preference (all recommendations are considered appropriate)	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for select patient populations (defined with recommendation).

Criteria

Prior authorization is required.

HER2-Positive Breast Cancer

Enhertu® is considered medically necessary when **ALL** of the following are met:

1. Diagnosis of recurrent, unresectable, or stage IV (M1) metastatic breast cancer that is human epidermal growth factor receptor 2 (HER2)-positive; **AND**
2. Member has received a prior anti-HER2-based regimen (either a *or* b):
    a. In the metastatic setting; or
    b. In the neoadjuvant or adjuvant setting and has rapid disease progression within 6 months of completing therapy (12 months for pertuzumab-containing regimens); **AND**
3. Member is 18 years of age or older; **AND**
4. Prescribed by, or in consultation with, an oncologist; **AND**
5. Request meets one of the following (a or b):
    a. Regimen prescribed does not exceed 5.4 mg/kg every 3 weeks (21-day cycle); or
    b. Regimen is supported by clinical practice guidelines (i.e., must be recommended in NCCN Guidelines®). Supporting clinical documentation must be provided with any request for which regimen prescribed does not align with FDA-approved labeling.

HER2-Low (IHC 1+ or IHC 2+/ISH-) Breast Cancer

Enhertu® is considered medically necessary when **ALL** of the following are met:

1. Diagnosis of recurrent, unresectable, or stage IV (M1) metastatic breast cancer that is human epidermal growth factor receptor 2 (HER2)-low (IHC 1+ or IHC 2+/ISH-); **AND**
2. Member has received a prior chemotherapy:
    a. In either the metastatic setting, or in the adjuvant setting and member has disease recurrence within 6 months of completing therapy; **AND**
    b. If tumor is hormone-receptor (HR)-positive, disease is refractory to endocrine therapy; **AND**
3. Member is 18 years of age or older; **AND**
4. Prescribed by, or in consultation with, an oncologist; **AND**
5. Request meets one of the following (a or b):
    a. Regimen prescribed does not exceed 5.4 mg/kg every 3 weeks (21-day cycle); or
    b. Regimen is supported by clinical practice guidelines (i.e., must be recommended in NCCN Guidelines®). Supporting clinical documentation must be provided with any request for which regimen prescribed does not align with FDA-approved labeling.

Non-Small Cell Lung Cancer (NSCLC)

Enhertu® is considered medically necessary when **ALL** of the following are met:

1. Diagnosis of unresectable or metastatic non-small cell lung cancer (NSCLC); **AND**
2. Presence of activating human epidermal growth factor receptor 2 (HER2) (ERBB2) mutations in tumor or plasma specimens (if no mutation is detected in a plasma specimen, test tumor tissue); **AND**
3. Failure of one prior line of systemic therapy; **AND**
4. Member is 18 years of age or older; **AND**
5. Prescribed by, or in consultation with, an oncologist; **AND**
6. Request meets one of the following (a or b):
    a. Regimen prescribed does not exceed 5.4 mg/kg every 3 weeks (21-day cycle); or
    b. Regimen is supported by clinical practice guidelines (i.e., must be recommended in NCCN Guidelines®). Supporting clinical documentation must be provided with any request for which regimen prescribed does not align with FDA-approved labeling.

HER2-Positive Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma

Enhertu® is considered medically necessary when **ALL** of the following are met:

1. Diagnosis of locally advanced or metastatic gastric or gastroesophageal junction (GEJ) cancer that has human epidermal growth factor receptor 2 (HER2)-protein overexpression or HER2 gene amplification; **AND**
2. Failure of a prior trastuzumab-based regimen; **AND**
3. Member is 18 years of age or older; **AND**
4. Prescribed by, or in consultation with, an oncologist; **AND**
5. Request meets one of the following (a or b):
    a. Regimen prescribed does not exceed 6.4 mg/kg every 3 weeks (21-day cycle); or
    b. Regimen is supported by clinical practice guidelines (i.e., must be recommended in NCCN Guidelines®). Supporting clinical documentation must be provided with any request for which regimen prescribed does not align with FDA-approved labeling.

Continuation Criteria (all indications)

Enhertu® is considered medically necessary for continuation of therapy when **ALL** of the following are met:

1. Member is currently receiving medication through the Iowa Medicaid benefit or has previously met initial approval criteria; **AND**
2. Documentation of positive clinical response to therapy, as demonstrated by tumor response or lack of disease progression, and an acceptable toxicity profile; **AND**
3. Prescribed by, or in consultation with, an oncologist; **AND**
4. The regimen prescribed is within the FDA-approved labeling. If dose or schedule exceeds the FDA-approved labeling, therapy regimen (including dosage) must be supported by clinical practice guidelines (i.e., must be recommended in the NCCN Clinical Practice Guidelines®). Supporting clinical documentation must be provided with any request for which the regimen or dosage prescribed does not align with FDA-approved labeling.

Approval Duration and Quantity Limits

Approval Duration	Initial Authorization: 6 months Subsequent Authorization(s): 12 months		
Quantity Limits	Metastatic breast cancer	5.4 mg/kg	once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity
	Unresectable or metastatic HER2-mutant NSCLC		
	Locally advanced or metastatic gastric cancer	6.4 mg/kg	

Coding and Product Information

The following list(s) of codes and product information are provided for reference purposes only and may not be all inclusive. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment, nor does the exclusion of a code imply that its association to the HCPCS code is inappropriate.

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

ICD-10	Description
C16.0 – C16.9	Gastric cancer: specific codes indicate primary site, e.g., C16.4 indicates malignant neoplasm of pylorus (additional ICD-10 codes apply identifying the location of the metastasis)
C34.10 – C34.92	Bronchus and lung cancer: specific codes indicate primary site, e.g., C34.10 indicates malignant neoplasm of upper lobe, unspecified bronchus or lung (additional ICD-10 codes apply identifying the location of the metastasis)
C50.011 – C50.929	Breast cancer: specific codes indicate primary site, e.g., C50.211 indicates malignant neoplasm of upper-inner quadrant of right female breast (additional ICD-10 codes apply identifying the location of the metastasis)

NDC	Labeler	Dosage	Pkg Size	Pkg Qty	Units/Pkg
65597-0406-01	Daiichi Sankyo, Inc. (65597)	1 mg	1	EA	100

Compliance

1. Should conflict exist between this policy and applicable statute, the applicable statute shall supersede.
2. Federal and State law, as well as contract language, including definitions and specific contract provisions or exclusions, take precedence over medical policy and must be considered first in determining eligibility for coverage.
3. Medical technology is constantly evolving, and Iowa Medicaid reserves the right to review and update medical policy on an annual or as-needed basis.

Medical necessity guidelines have been developed for determining coverage for member benefits and are published to provide a better understanding of the basis upon which coverage decisions are made. Medical necessity guidelines are developed for selected physician-administered medications found to be safe and proven to be effective in a limited, defined population or clinical circumstances. They include concise clinical coverage criteria based on current literature review, consultation with practicing physicians in the service area who are medical experts in the particular field, FDA and other government agency policies, and standards adopted by national

accreditation organizations. Criteria are revised and updated annually, or more frequently if new evidence becomes available that suggests needed revisions.

References

[1] Enhertu prescribing information (11/2022). Daiichi Sankyo, Inc.: Basking Ridge, NJ. Available online at www.enhertuhcp.com. Accessed December 4, 2023.

[2] Wolff AC, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology /College of American Pathologists Clinical Practice Guideline Focused Update. Arch Pathol Lab Med. 2018 Nov;142(11):1364-1382. Epub 2018 May 30. PMID: 29846104.

[3] Yamauchi H, Bleiweiss IJ. HER2 and predicting response to therapy in breast cancer. Vora SR, ed. UpToDate. Waltham, MA: UpToDate Inc. www.uptodate.com. Accessed September 9, 2023.

[4] Joe BN. Clinical features, diagnosis, and staging of newly diagnosed breast cancer. Vora SR, ed. UpToDate. Waltham, MA: UpToDate Inc. www.uptodate.com. Accessed December 29, 2022.

[5] American Cancer Society: Cancer Statistics Center. State of Iowa. Available online at cancerstatisticscenter.cancer.org/#!/state/Iowa. Accessed December 29, 2022.

[6] Referenced from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer (v.5.2023 – November 8, 2023). Accessed December 8, 2023. The NCCN Guidelines® are a work in progress that may be refined as often as new significant data becomes available. To view the most recent and complete version of the guidelines, go online to NCCN.org.

[7] National Comprehensive Cancer Network (NCCN). Development and Update of Guidelines. Available online at www.nccn.org. Accessed October 11, 2023.

[8] Referenced from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer (v.4.2023 – March 23, 2023). Accessed December 4, 2023. The NCCN Guidelines® are a work in progress that may be refined as often as new significant data becomes available. To view the most recent and complete version of the guideline, go online to NCCN.org.

[9] Referenced from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Esophageal and Esophagogastric Junction Cancers (v.3.2023 – August 29, 2023). Accessed December 4, 2023. The NCCN Guidelines® are a work in progress that may be refined as often as new significant data becomes available. To view the most recent and complete version of the guideline, go online to NCCN.org.

[10] Referenced from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gastric Cancer (v.2.2023 – August 29, 2023). Accessed December 4, 2023. The NCCN Guidelines® are a work in progress that may be refined as often as new significant data becomes available. To view the most recent and complete version of the guideline, go online to NCCN.org.

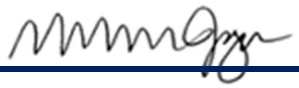
[11] Referenced from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer (v.5.2023 – November 8, 2023). Accessed December 4, 2023. The NCCN Guidelines® are a work in progress that may be refined as often as new significant data becomes available. To view the most recent and complete version of the guideline, go online to NCCN.org.

Development of utilization management criteria may also involve research into other state Medicaid programs, other payer policies, consultation with experts and review by the Medicaid Clinical Advisory Committee (CAC). These sources may not be referenced individually unless they are specifically published and are otherwise applicable to the criteria at issue.

Criteria Change History

Change Date	Changed By	Description of Change	Version
[mm/dd/yyyy]			
Signature			

Change Date	Changed By	Description of Change	Version
[mm/dd/yyyy]			
Signature			

Change Date	Changed By	Description of Change	Version
01/19/2024	CAC	Annual review. Added overview of Lung Cancer to Descriptive Narrative. Updated NCCN Guidelines. Added dosing information into criteria.	4
Signature William (Bill) Jagiello, DO			
Change Date	**Changed By**	**Description of Change**	**Version**
01/20/2023	CAC	Added criteria for new indications: HER2-low metastatic breast cancer (FDA-approved 8/5/22); unresectable or metastatic HER2-Mutant NSCLC (FDA-approved via accelerated approval on 8/11/22). Updated HER2-positive breast cancer criteria to include rapid disease progression. Updated NCCN Guidelines® recommendations. Added section on patient selection.	3
Signature William (Bill) Jagiello, DO			
Change Date	**Changed By**	**Description of Change**	**Version**
04/15/2022	CAC	Annual review. Rewrite.	2
Signature William (Bill) Jagiello, DO			
Change Date	**Changed By**	**Description of Change**	**Version**
04/16/2021	CAC	Criteria implementation.	1
Signature William (Bill) Jagiello, DO			

CAC = Medicaid Clinical Advisory Committee