Clinical Policy: Fam-Trastuzumab Deruxtecan-nxki (Enhertu)

Reference Number: LA.PHAR.456
Effective Date: 10.05.24
Last Review Date: 06.23.25~~10.04.24~~ Coding Implications
Line of Business: Medicaid Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

****Please note: This policy is for medical benefit****

Description
Fam-trastuzumab deruxtecan-nxki (Enhertu®) is a human epidermal growth factor receptor 2 (HER2)-directed antibody and topoisomerase inhibitor conjugate.

FDA Approved Indication(s)
Enhertu is indicated for the treatment of adult patients with:

- 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 setting and have developed disease recurrence during or within six months of completing therapy.
- 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.
- 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*.
- Locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.
- Unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no statisfactory alternative treatment options.*

**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.*

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of Louisiana Healthcare Connections that Enhertu is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. IHC 3+ Solid Tumors (must meet all):
1. Diagnosis of HER2-positive, IHC 3+ solid tumor (*see Appendix D*);
2. Disease is unresectable or metastatic;
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;
5. Failure of at least one prior line of standard systemic regimen for the disease, or have no available standard treatment as a satisfactory alternative treatment option;
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 5.4 mg/kg every 3 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 6 months

B. Breast Cancer (must meet all)**:**
1. Diagnosis of recurrent, unresectable, or metastatic breast cancer that is one of the following (a or b):
   a. HER2-positive;
   b. HER2-low (IHC 1+ or IHC 2+/ISH-);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Member meets one of the following (a or b):
   a. For HER2-positive breast cancer, one of the following (i or ii):
      i. Failure of one prior anti-HER2-based regimen (*see Appendix B*), unless contraindicated or clinically significant adverse effects are experienced;
      ii. Rapid disease progression within 6 months of neoadjuvant or adjuvant therapy (12 months for pertuzumab-containing regimens);

      **Prior authorization may be required for anti-HER2-based regimens*
   b. For HER2-low (IHC 1+ or IHC2+/ISH-) breast cancer, one of the following (i or ii):
      i. Failure of at least one prior line of chemotherapy (if hormone-receptor [HR]-positive, previous therapy should include an endocrine therapy, unless ineligible or the member has visceral crisis) (*see Appendix B for examples*);
      ii. Disease recurrence during or within 6 months of completing adjuvant chemotherapy;
5. Request meets one of the following (a or b):*
   a. Dose does not exceed 5.4 mg/kg every 3 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 6 months

C. Gastric and Gastroesophageal Junction Cancer (must meet all)**:**
1. Diagnosis of HER2-positive gastric or GEJ adenocarcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;

4. Disease is locally advanced, recurrent, or metastatic;
5. Failure of a trastuzumab-based regimen (*see Appendix B*);
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 6.4 mg/kg every 3 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 6 months

D. Non-Small Cell Lung Cancer (must meet all)**:**
1. Diagnosis of unresectable or metastatic NSCLC;
2. Disease has activating HER2 (ERBB2) mutations;
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;
5. Failure of one prior line of chemotherapy (*see Appendix B for examples*);
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 5.4 mg/kg every 3 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 6 months

E. Colon or Rectal Cancer (off label) (must meet all):
1. Diagnosis of advanced or metastatic colon or rectal cancer, including appendiceal adenocarcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Member meets one of the following (a or b):
   a. Documentation supports failure of or presence of clinically significant adverse effects or contraindication to at least two FDA approved medications for the relevant diagnosis (e.g., oxaliplatin, irinotecan, FOLFOX [fluorouracil, leucovorin, and oxaliplatin] or CapeOX [capecitabine and oxaliplatin], bevacizumab);
   b. Enhertu is prescribed as adjuvant therapy for rectal cancer as a single agent for unresectable metachronous metastases (HER2-amplified and RAS and BRAF wild-type) (proficient mismatch repair/microsatellite-stable [pMMR/MSS] only) that converted to resectable disease after initial treatment;
5. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 6 months

F. Other NCCN Recommended Uses (off-label) (must meet all)**:**
1. Diagnosis of one of the following (a, b, or c):
   a. Recurrent or metastatic HER2-positive cervical cancer;
   b. Recurrent HER2-positive salivary gland tumors;

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c. Recurrent or metastatic HER2-positive endometrial carcinoma;
2. Prescribed or in consultation with an oncologist;
3. Age ≥ 18 years;
4. For cervical cancer: Prescribed as a single agent following failure of ≥ 1 prior therapy (see *Appendix B*);
5. For salivary gland tumors: Prescribed as a single agent and member has one of the following (a or b):
   a. Distant metastases in patients with a performance status (PS) of 0-3;
   b. Unresectable locoregional recurrence or second primary with prior radiation therapy;
6. For endometrial carcinoma: Prescribed as a single agent following failure of ≥ 1 prior therapy (see *Appendix B*);
7. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 6 months

G. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to LA.PMN.255
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy ~~for the relevant line of business:~~ LA.PMN.53 ~~for Medicaid~~.

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via Louisiana Healthcare Connections benefit, or documentation supports that member is currently receiving Enhertu for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a, b, or c):*
   a. For breast cancer, NSCLC, or IHC 3+ solid cancers: New dose does not exceed 5.4 mg/kg every 3 weeks;
   b. For gastric or GEJ adenocarcinoma: New dose does not exceed 6.4 mg/kg every 3 weeks;
   c. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to LA.PMN.255

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy ~~for the relevant line of business:~~ LA.PMN.53 ~~for Medicaid~~.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policy – LA.PMN.53 ~~for Medicaid, or evidence of coverage documents~~.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
GEJ: gastroesophageal junction
HER2: human epidermal growth factor receptor 2
- HR: hormone-receptor
IHC: immunohistochemistry (assay)
NCCN: National Comprehensive Center Network
NSCLC: non-small cell lung cancer

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Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
HER2+ Breast Cancer NCCN examples of systemic therapies for recurrent or metastatic disease: • Aromatase inhibitor ± trastuzumab • Aromatase inhibitor ± lapatinib • Pertuzumab + trastuzumab + docetaxel	Varies	Varies
Breast Cancer • Examples of systemic therapies include but are not limited to: eribulin, capecitabine, gemcitabine, nab-paclitaxel, paclitaxel • Examples of endocrine therapies for HR+ disease include but are not limited to: sacituzumab, palbociclib, ribociclib, abemacicilib, tamoxifen, letrozole, anastrozole, exemestane	Varies	Varies
Gastric and Gastroesophageal Junction Cancer trastuzumab-based regimen	8 mg/kg IV followed by 6 mg/kg IV q 3 weeks	8 mg/kg
NSCLC	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Examples of systemic therapies include but are not limited to: • Carboplatin or cisplatin + pemetrexed + pembrolizumab • Carboplatin + paclitaxel + bevacizumab + atezolizumab • Carboplatin + albumin-bound paclitaxel + atezolizumab • Carboplatin + paclitaxel or albumin-bound paclitaxel + pembrolizumab • Nivolumab + ipilimumab + paclitaxel + carboplatin or cisplatin Examples of targeted therapies include but are not limited to: • EGFR mutation positive: afatinib, erlotinib, dacomitinib, gefitinib, osimertinib, erlotinib + ramucirumab, erlotinib + bevacizumab (non-squamous) • BRAF: dabrafenib/trametinib, dabrafenib, vemurafenib • ALK: alectinib, brigatinib, ceritinib, crizotinib, lorlatinib ROS1: ceritinib, crizotinib, entrectinib		
Cervical Cancer Examples of first-line therapies include but are not limited to: • Cisplatin or carboplatin + paclitaxel ± bevacizumab • Topotecan + paclitaxel ± bevacizumab • Cisplatin + topotecan • Cisplatin • Carboplatin Examples of NCCN-preferred second-line or subsequent therapies include but are not limited to: • Tisotumab vedotin-tftv • Cemiplimab • Bevacizumab • Paclitaxel • Albumin-bound paclitaxel • Docetaxel	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
• Fluorouracil • Gemcitabine • Pemetrexed • Topotecan • Vinorelbine • Irinotecan		
Endometrial Carcinoma Examples of first-line therapies include but are not limited to: • Carboplatin + paclitaxel + trastuzumab • Carboplatin + docetaxel • Carboplatin + paclitaxel + bevacizumab Examples of NCCN-preferred second-line or subsequent therapies include but are not limited to: • Cisplatin + doxorubicin • Cisplatin + doxorubicin + paclitaxel • Cisplatin • Carboplatin • Doxorubicin • Liposomal doxorubicin • Paclitaxel • Albumin-bound paclitaxel • Topotecan • Bevacizumab • Temsirolimus • Cabozantinib • Docetaxel • Ifosfamide (for carcinosarcoma) • Ifosfamide + paclitaxel (for carcinosarcoma) • Cisplatin + ifosfamide	Varies	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings
- Contraindication(s): none reported
- Boxed warning(s): interstitial lung disease and pneumonitis; embryo-fetal toxicity

Appendix D: IHC 3+ Solid Tumors
- In DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02 clinical trials, the following were solid tumor types that were included in the study: colorectal cancer,

bladder cancer, biliary tract cancer, NSCLC, endometrial cancer, ovarian cancer, cervical cancer, salivary gland cancer, pancreatic cancer, orophanryngeal neoplasm, vulvar cancer, extramammary Paget's disease, lacrimal gland cancer, lip and/or oral cavity cancer, esophageal adenocarcinoma, and esophageal squamous cell carcinoma.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Breast cancer, NSCLC, ICH 3+ solid tumors	5.4 mg/kg IV every 3 weeks	5.4 mg/kg
Gastric, GEJ cancer	6.4 mg/kg IV every 3 weeks	6.4 mg/kg

VI. Product Availability

Single-dose vial: 100 mg lyophilized powder

VII. References

1. Enhertu Prescribing Information. Basking Ridge, NJ: Daiichi Sankyo, Inc.; April 2024. Available at: www.enhertu.com. Accessed ~~May 31~~October 21, 2024.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at http://www.nccn.org/professionals/drug_compendium. Accessed ~~May 31~~December 2, 2024.
3. Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med*. 2019; doi: 10.1056/NEJMoa1914510.

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Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

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

Reviews, Revisions, and Approvals	Date	LDH Approval Date
Converted corporate to local policy.	04.22	07.01.22
Added criteria for new FDA-approved indication as 2nd line for breast cancer per PI; added criteria for 1st-line therapy for breast cancer in select patients per NCCN. Added criteria for new FDA-approved indications for NSCLC and HER2-low breast cancer. Template changes applied to other diagnoses/indications. Added off-label use for advanced or metastatic colon and rectal cancers per NCCN; added recurrent gastric or GEJ cancer as a covered indication per NCCN. Added language to the FDA Approved Indications section re: using an FDA-approved test to identify HER2-low breast cancer; references reviewed and updated. Added blurb this policy is for medical benefit only.	06.27.23	10.05.23

Reviews, Revisions, and Approvals	Date	LDH Approval Date
Per NCCN guidelines, clarified that off-label use for appendiceal adenocarcinoma is included as a colorectal cancer, added criteria for use as adjuvant therapy in rectal cancer, added criteria for off-label use for cervical cancer, salivary gland tumors, and endometrial carcinoma; references reviewed and updated.	05.27.24	08.20.24
Added newly approved indication for IHC 3+ solid tumors.	10.04.24	01.27.25
Annual review: per NCCN guidelines for HER2-low breast cancer added a bypass of prior endocrine therapy for HR-positive disease if the member has visceral crisis; references reviewed and updated.	06.23.25	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. LHCC makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable LHCC administrative policies and procedures.

This clinical policy is effective as of the date determined by LHCC. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. LHCC retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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