Enhertu® (fam-trastuzumab deruxtecan-nxki)
(Intravenous)

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Document Number: IC-0540

Last Review Date: 10/01/2020
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Dates Reviewed: 06/2020, 07/2020, 10/2020

I. Length of Authorization

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

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Enhertu 100 mg vial – 6 vials every 21 days

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

- 600 billable units every 21 days

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient at least 18 years of age; **AND**

Universal Criteria

- Left ventricular ejection fraction (LVEF) is within normal limits prior to initiating therapy and will be assessed at regular intervals (e.g., every 3 months) during treatment; **AND**
- Patient has human epidermal growth factor receptor 2 (HER2)-positive* disease; **AND**
- Used as single agent therapy; **AND**
- Therapy will not be substituted with or for any trastuzumab-based formulation (i.e., trastuzumab [or trastuzumab biosimilar product], ado-trastuzumab emtansine, trastuzumab-hyaluronidase, pertuzumab/trastuzumab and hyaluronidase-zzxf, etc.); **AND**

Breast Cancer † [1,2,4,8]

- Patient has unresectable or metastatic disease; **AND**
- Patient was previously treated with ado-trastuzumab emtansine (T-DM1) and at least one other anti-HER2-based regimens (i.e., trastuzumab, pertuzumab, lapatinib, etc.) for metastatic disease

Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

† FDA approved indication(s), ‡ Compendia Recommended Indication(s)

*HER2-positive overexpression criteria:[7,8]

• Immunohistochemistry (IHC) assay 3+; **OR**
• Dual-probe in situ hybridization (ISH) assay HER2/CEP17 ratio ≥ 2.0 AND average HER2 copy number ≥ 4.0 signals/cell; **OR**
• Dual-probe in situ hybridization (ISH) assay AND concurrent IHC indicating one of the following:
  ○ HER2/CEP17 ratio ≥ 2.0 AND average HER2 copy number < 4.0 signals/cell AND concurrent IHC 3+; **OR**
  ○ HER2/CEP17 ratio < 2.0 AND average HER2 copy number ≥ 6.0 signals/cell AND concurrent IHC 2+ or 3+; **OR**
  ○ HER2/CEP17 ratio < 2.0 AND average HER2 copy number ≥ 4.0 and < 6.0 signals/cell AND concurrent IHC 3+

IV. Renewal Criteria [1]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: left ventricular dysfunction/symptomatic congestive heart failure, pulmonary toxicity (i.e., interstitial lung disease/pneumonitis), neutropenia/febrile neutropenia, etc.; **AND**
  - LVEF is > 45% and <u>absolute</u> decrease is ≤ 20% from baseline (LVEF results must be within the previous 3 months); **OR**
  - LVEF is 40% to 45% and <u>absolute</u> decrease is < 10% from baseline (LVEF results must be within the previous 3 months)

V. Dosage/Administration

Indication	Dose
Breast Cancer	Administer 5.4 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity

VI. Billing Code/Availability Information

<u>HCPCS Code:</u>

- J9358 - Injection, fam-trastuzumab deruxtecan-nxki, 1 mg: 1 billable unit = 1 mg

<u>NDC:</u>

- Enhertu 100 mg single-use vial: 65597-0406-xx

VII. References (STANDARD)

1. Enhertu [package insert]. Basking Ridge, NJ; Daiichi Sankyo, Inc; December 2019. Accessed September 2020.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) fam-trastuzumab deruxtecan. National Comprehensive Cancer Network, 2020. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed September 2020.
3. Fahrenbruch R, Kintzel P, Bott AM, et al. Dose Rounding of Biologic and Cytotoxic Anticancer Agents: A Position Statement of the Hematology/Oncology Pharmacy Association. J Oncol Pract. 2018 Mar;14(3):e130-e136.
4. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer 6.2020. National Comprehensive Cancer Network, 2020. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed September 2020.
5. Wolff AC, Hammond EH, Allison KH, 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. J Clin Oncol 2018;36:2105-2122.
6. Hematology/Oncology Pharmacy Association (2019). *Intravenous Cancer Drug Waste Issue Brief*. Retrieved from http://www.hoparx.org/images/hopa/advocacy/Issue-Briefs/Drug_Waste_2019.pdf
7. Bach PB, Conti RM, Muller RJ, et al. Overspending driven by oversized single dose vials of cancer drugs. BMJ. 2016 Feb 29;352:i788.
8. Modi S, Saura C, Yamashita T, et al; DESTINY-Breast01 Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. N Engl J Med. 2019 Dec 11. doi: 10.1056/NEJMoa1914510.
9. First Coast Service Options, Inc. Local Coverage Article: Billing and Coding: Trastuzumab - Trastuzumab Biologics (A56660). Centers for Medicare & Medicaid Services, Inc. Updated on 7/22/2020 with effective date of 7/1/2020. Accessed August 2020.

VIII. References (ENHANCED)

10. Krop IE, Kim SB, Martin AG, et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. Lancet Oncol. 2017;18(6):743–754.
11. Cameron D, Casey M, Oliva C, Newstat B, Imwalle B, Geyer CE. Lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer: final survival analysis

of a phase III randomized trial. Oncologist. 2010;15(9):924–934. doi:10.1634/theoncologist.2009-0181.

12. Blackwell KL, Burstein HJ, Storniolo AM, et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. J Clin Oncol. 2012 Jul 20;30(21):2585-92. doi: 10.1200/JCO.2011.35.6725. Epub 2012 Jun 11.
13. von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. J Clin Oncol. 2009 Apr 20;27(12):1999-2006. doi: 10.1200/JCO.2008.19.6618. Epub 2009 Mar 16.
14. Magellan Health, Magellan Rx Management. Enhertu Clinical Literature Review Analysis. Last updated September 2020. Accessed September 2020.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
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

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs) and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at:

http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA):

Jurisdiction(s): N(9)	**NCD/LCD/LCA Document (s):** A56660
https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A56660&bc=EAAAAAAAAAAA&SearchType=Advanced	

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC

Appendix 3 – CLINICAL LITERATURE REVIEW

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; DoR = duration of response; TTP = time to progression; FFS = failure-free survival; EFS = event-free survival; PFR = progression free rate; T-DM1 = trastuzumab emtansine; NR = not reached

Breast Cancer

HER2-positive metastatic disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Fam-trastuzumab deruxtecan-nxki	2A	Yes (after 2 or more prior anti-HER2-based regimens)	Phase 2 (DESTINY-Breast01), open-label, single-arm	N/A	ORR	≥ 2 prior therapies including T-DM1	• Trastuzumab deruxtecan showed durable antitumor activity in a pretreated patient population with HER2-positive metastatic breast cancer with an ORR 60.9% and duration of response of 14.8 months.
Ado-trastuzumab emtansine (T-DM1)	2A	Yes (After prior trastuzumab and a taxane. Patients should have either received prior therapy for metastatic disease or developed disease recurrence	Phase 3 (TH3RESA), randomized, parallel assessment, open-label	Treatment of physician's choice (TPC)	PFS OS	Third-line therapy or later after at least two HER2-directed regimens in the advanced setting (with progression on both trastuzumab- and lapatinib-containing regimens)	• Patients who had progressed on two or more HER2-directed regimens, T-DM1 treatment resulted in a significant improvement in OS versus TPC

		during or within 6 months of completing adjuvant therapy)					
Lapatinib+ capecitabine	2A	Yes	Phase 3, randomized	Capecitabine alone	TTP	Second-line therapy or later after prior trastuzumab (metastatic setting) and prior treatment with an anthracycline and a taxane (metastatic or adjuvant setting)	• Lapatinib+ capecitabine demonstrated a significant benefit in TTP and a trend towards an improvement in OS compared to capecitabine alone
Trastuzumab+ lapatinib	2A	No	Phase 3 (EGF104900 Study), randomized, open-label	Lapatinib monotherapy	PFS	Second-line therapy or later after one or more prior trastuzumab-containing regimens for metastatic disease	• Modest improvement (3 weeks) in PFS with lapatinib+ trastuzumab versus lapatinib alone • 4.5mon OS advantage with lapatinib+ trastuzumab in patients with pretreated HER2-positive metastatic breast cancer
Trastuzumab+ capecitabine	2A	No	Phase 3 (TBP), randomized	Capecitabine	TTP	After prior trastuzumab-based therapy (in adjuvant or metastatic setting)	• Continuing trastuzumab and adding capecitabine beyond trastuzumab progression showed a significant improvement in ORR and TTP compared with capecitabine alone • However, difference in OS was not significant