

Clinical Criteria

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Subject: Enhertu (fam-trastuzumab deruxtecan-nxki)

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Overview

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This document addresses the use of Enhertu (fam-trastuzumab deruxtecan-nxki). Enhertu is HER2-directed antibody and topoisomerase inhibitor conjugate that selectively delivers chemotherapy to HER2-overexpressing tumor cells. Internalization and intracellular linker cleavage of the drug by lysosomal enzymes within the tumor cell leads to DNA damage and apoptotic cell death.

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Breast cancer is a type of tumor comprised of malignant (cancerous) cells that start to grow in the breast and may spread (metastasize) to surrounding tissues and other areas of the body (American Cancer Society, 2016). Breast cancer is commonly treated by various modalities which include combinations of surgery, radiation therapy, chemotherapy and hormone therapy (National Cancer Institute, 2019). The prognosis and selection of therapies can be affected by clinical and pathologic features of the tumor. One of these includes the human epidermal growth factor receptor 2 gene ERBB2 which is commonly referred to as HER2. Other names for this gene include NEU, Her-2, HER-2/neu and c-erb B2. Initially the HER2 gene was detected in frozen breast tumor samples. Amplification of the HER2 gene was later correlated to overexpression of protein levels in samples of breast cancer.

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Approximately 255,000 patients are diagnosed with invasive breast cancer each year, with approximately one in five cases being classified as HER-2 positive. Antibody-drug conjugates containing trastuzumab and a second non-specific cytotoxic drug have the ability to more specifically target HER-2 cancer cells and exert their anti-tumor effects. Kadcyla and Enhertu are currently the only two HER2-directed antibody-drug conjugates on the market. Kadcyla is linked to emtansine, a tubulin inhibitor, whereas Enhertu is linked to DXd, a topoisomerase inhibitor.

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The FDA approved indications for Enhertu use as a single agent to treat those with HER2-positive, metastatic breast cancer who previously received two or more prior anti-HER2-based regimens in the metastatic setting.

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The National Comprehensive Cancer Network® (NCCN) currently does not provide recommendations for Enhertu's place in therapy. Herceptin (trastuzumab) plus Perjeta (pertuzumab) and docetaxel (category 1) or paclitaxel (category 2A) are considered preferred first line regimens. Second line agents include other trastuzumab containing regimens, including the second HER2-directed antibody-drug conjugate Kadcyla (ado-trastuzumab emtansine) (category 2A).

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Enhertu has a black box warning for interstitial lung disease and embryo-fetal toxicity. Interstitial lung disease (ILD) and pneumonitis, including fatal 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.

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Definitions and Measures

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HER2 testing (adapted from American Society of Clinical Oncology/College of American Pathologists):

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Positive HER2:

- IHC 3+ based on circumferential membrane staining that is complete, intense. (Observed in a homogeneous and contiguous population and within > 10% of the invasive tumor cells).
- ISH positive based on:
 - Single-probe average HER2 copy number \geq 6.0 signals/cell*
 - Dual-probe HER2/CEP 17 ratio \geq 2.0* with an average HER2 copy number \geq 4.0 signals/cell

- Dual-probe HER2/CEP17 ratio $\geq 2.0^*$ with an average HER2 copy number < 4.0 signals/cell
- Dual-probe HER2/CEP17 ratio $< 2.0^*$ with an average HER2 copy number ≥ 6.0 signals/cell

* (Observed in a homogeneous and contiguous population and within $>10\%$ of the invasive tumor cells. By counting at least 20 cells within the area)

Equivocal HER2:

- IHC 2+ based on circumferential membrane staining that is incomplete and/or weak/moderate and within $>10\%$ of the invasive tumor cells or complete and circumferential membrane staining that is intense and within $\leq 10\%$ of the invasive tumor cells.
- ISH equivocal based on:
 - Single-probe average HER2 copy number ≥ 4.0 and < 6.0 signals/cell
 - Dual-probe HER2/CEP17 ratio < 2.0 with an average HER2 copy number ≥ 4.0 signals/cell

Negative HER2 if a single test (or both tests) performed show:

- IHC 1+ as defined by incomplete membrane staining that is faint/barely perceptible and within $> 10\%$ of the invasive tumor cells
- IHC 0 as defined by no staining observed or membrane staining that is incomplete and is faint/barely perceptible and within $\leq 10\%$ of the invasive tumor cells
- ISH negative based on:
 - Single-probe average HER2 copy number < 4.0 signals/cell
 - Dual-probe HER2/CEP17 ratio < 2.0 with an average HER2 copy number < 4.0 signals/cell

Metastasis: The spread of cancer from one part of the body to another; a metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.

Monoclonal antibody: A protein developed in the laboratory that can locate and bind to specific substances in the body and on the surface of cancer cells.

Progressive Disease (PD): Cancer that is growing, spreading, or getting worse.

Refractory Disease: Illness or disease that does not respond to treatment.

Targeted biologic agent: A newer type of drug developed specifically to target genetic changes in cells that cause cancer. It works differently than standard chemotherapy drugs, often with different side effects.

Unresectable: Unable to be removed with surgery.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Enhertu (fam-trastuzumab deruxtecan-nxki)

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

- I. Individual has a diagnosis of unresectable or metastatic HER2-positive (HER2+) breast cancer (NCCN 1) confirmed by one of the following:
 - A. Immunohistochemistry (IHC) is 3+; OR
 - B. In situ hybridization (ISH) positive; AND
- II. Individual is using as monotherapy; AND
- III. Individual has had at least two or more prior anti-HER2 therapies in the metastatic phase of breast cancer;

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

- I. When the above criteria are not met and for all other indications; OR
- II. When Enhertu is used in combination with other targeted biologic agents or chemotherapy agents.

Coding

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