CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Pertuzumab, Trastuzumab, and Hyaluronidase-zzxf (Phesgo®)

Version: 1.0

EFFECTIVE DATE: 8/28/2025

NantHealth® | Eviti®

Please note the following:

For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Pertuzumab, trastuzumab, and hyaluronidase-zzxf (Phesgo®)

Discussion

Pertuzumab targets the extracellular dimerization domain (subdomain II) of HER2 and, thereby, blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3 and HER4. As a result, pertuzumab inhibits ligand-initiated intracellular signaling through two major signaling pathways, mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K). Inhibition of these signaling pathways can result in cell growth arrest and apoptosis, respectively.

Trastuzumab binds to subdomain IV of the extracellular domain of the HER2 protein to inhibit the ligand-independent, HER2 mediated cell proliferation and PI3K signaling pathway in human tumor cells that overexpress HER2.

Both pertuzumab and trastuzumab-mediated antibody-dependent cell-mediated cytotoxicity (ADCC) have been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2. While pertuzumab alone inhibited the proliferation of human tumor cells, the combination of pertuzumab and trastuzumab augmented anti-tumor activity in HER2-overexpressing xenograft models.

Hyaluronan is a polysaccharide found in the extracellular matrix of the subcutaneous tissue. It is depolymerized by the naturally occurring enzyme hyaluronidase. Unlike the stable structural components of the interstitial matrix, hyaluronan has a half-life of approximately 0.5 days. Hyaluronidase increases permeability of the subcutaneous tissue by depolymerizing hyaluronan.

Boxed warnings include cardiomyopathy, embryo-fetal toxicity, and pulmonary toxicity. The most common adverse reactions include diarrhea, alopecia, neutropenia, anemia, asthenia, nausea, fatigue, and rash.[1]

Pertuzumab, trastuzumab, and hyaluronidase-zzxf is approved by the Food and Drug Administration (FDA) and the National Comprehensive Cancer Network (NCCN) for breast cancer.[1,2]

Definitions

- **Food and Drug Administration (FDA)** - The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.[3]
- **National Comprehensive Cancer Network (NCCN)** - An alliance of more than 30 leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.[4]

Policy

Coverage will be considered for FDA approved indications and for NCCN category 1, 2A, or 2B recommendations when the following criteria are met:

Breast Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Combination with chemotherapy for one of the following:
   a) Neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early-stage disease
   b) Adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence
4. Combination with docetaxel for the treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.[1]

Invasive Breast Cancer

For **NCCN** required criteria coverage:

5. Preoperative systemic therapy for patients with human epidermal growth factor receptor 2 (HER2)-positive tumors and locally advanced c≥T2 or cN+ and M0 disease or cT1c, cN0 disease as a component of or in combination with one of the following:
   a) TCHP (docetaxel, carboplatin, trastuzumab and pertuzumab)
   b) Paclitaxel, carboplatin and trastuzumab
   c) Trastuzumab and paclitaxel following AC (doxorubicin and cyclophosphamide) (dose-dense or every 3 weeks) regimen
   d) Trastuzumab and docetaxel following AC regimen
   e) Paclitaxel and trastuzumab

   Note: It is acceptable to change the administration sequence to taxane followed by AC; OR

6. Adjuvant systemic therapy for pT2-3 and pN0 or pN+ tumors for patients with human epidermal growth factor receptor 2 (HER2)-positive tumors as a component of or in combination with one of the following:
   a) TCHP (docetaxel, carboplatin, trastuzumab and pertuzumab) regimen
   b) Paclitaxel, carboplatin, and trastuzumab
   c) Trastuzumab and paclitaxel following AC (doxorubicin and cyclophosphamide) (dose-dense or every 3 weeks) regimen
   d) Trastuzumab and docetaxel following AC regimen.
   e) Paclitaxel and trastuzumab

Note:
1. It is acceptable to change the administration sequence to taxane followed by AC
2. If no residual disease after preoperative therapy or no preoperative therapy, complete up to one year of HER2 targeted therapy with trastuzumab with or without pertuzumab after completing planned chemotherapy regimen course. If residual disease is present after preoperative therapy and ado-trastuzumab emtansine is discontinued for toxicity, then trastuzumab with or without pertuzumab to complete one year of therapy can be used; OR

7. Adjuvant systemic therapy for patients with human epidermal growth factor receptor 2 (HER2)-positive tumors and locally advanced disease following completion of planned chemotherapy and following mastectomy or breast-conserving surgery (BCS) with surgical axillary staging, with trastuzumab if one of the following:
   a) ypT0N0 or pCR (especially if node positive at initial staging)
   b) ypT1-4N0 (if ado-trastuzumab discontinued for toxicity) (especially if node positive at initial staging)
   c) ypN≥1 (if ado-trastuzumab discontinued for toxicity) (especially if node positive at initial staging); OR

8. Recurrent unresectable (local or regional) or stage IV (M1) human epidermal growth factor receptor 2 (HER2)-positive disease that is either hormone receptor negative, or hormone receptor-positive for one of the following:
   a) First-line therapy in combination with trastuzumab with either docetaxel or paclitaxel
   b) In combination with trastuzumab with or without cytotoxic therapy (e.g., vinorelbine or taxane) for one line of therapy in patients previously treated with chemotherapy and trastuzumab in the absence of pertuzumab; OR

Inflammatory Breast Cancer

For **NCCN** required criteria coverage:

9. Preoperative systemic therapy for human epidermal growth factor receptor 2 (HER2)-positive disease as a component of or in combination with one of the following:
   a) TCHP (docetaxel, carboplatin, trastuzumab and pertuzumab)
   b) Paclitaxel, carboplatin and trastuzumab
   c) Trastuzumab and paclitaxel following AC (doxorubicin and cyclophosphamide) (dose-dense or every 3 weeks) regimen
   d) Trastuzumab and docetaxel following AC regimen
   e) Paclitaxel and trastuzumab

   Note: It is acceptable to change the administration sequence to taxane followed by AC; OR

10. Adjuvant systemic therapy for patients who had a response to preoperative systemic therapy, followed by surgery, and need to complete planned chemotherapy, for human epidermal growth factor receptor 2 (HER2)-positive pT2-3 and pN0 or pN+ tumors only as a component of or in combination with one of the following:
    a) TCHP (docetaxel, carboplatin, trastuzumab and pertuzumab)
    b) Paclitaxel, carboplatin and trastuzumab

a) Trastuzumab and paclitaxel following AC (doxorubicin and cyclophosphamide) (dose-dense or every 3 weeks) regimen
b) Trastuzumab and docetaxel following AC regimen
c) Paclitaxel and trastuzumab

Note:
1. It is acceptable to change the administration sequence to taxane followed by AC
2. If no residual disease after preoperative therapy, complete up to one year of HER2 targeted therapy with or without pertuzumab after completing the planned chemotherapy regimen. If residual disease is present after preoperative therapy and ado-trastuzumab emtansine is discontinued for toxicity, then trastuzumab with or without pertuzumab to complete one year of therapy can be used; OR

11. No response to preoperative systemic therapy, or recurrent unresectable (local or regional) or stage IV (M1) human epidermal growth factor receptor 2 (HER2)-positive disease that is either hormone receptor-negative, or hormone receptor-positive in combination with one of the following:
    a) First-line therapy of trastuzumab with either docetaxel or paclitaxel
    b) Trastuzumab with or without cytotoxic therapy (e.g., vinorelbine or taxane) for one line of therapy in patients previously treated with chemotherapy and trastuzumab in the absence of pertuzumab.[2]

Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

Coding (CPT®, ICD-10, and HCPCS)

Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment. CPT codes are available through the AMA.

Code	Description
C50	Breast cancer
C50.11	Malignant neoplasm of right female breast
C50.12	Malignant neoplasm of left female breast
C50.19	Malignant neoplasm 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
J9316	Injection, pertuzumab, trastuzumab, and hyaluronidase-zzxf

Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	8/28/2025
2	Policy Annual Review Dates:	
3	Department Owner:	Medical Affairs
4	NH Advisory Committee Approval Dates:	8/28/2025
5	Revision Changes:	

References

[1] Phesgo (Pertuzumab, Trastuzumab, and Hyaluronidase-zzxf) [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761170s007lbl.pdf. Accessed July 14, 2025.

[2] National Comprehensive National Cancer Network. NCCN Guidelines: Breast Cancer. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed July 14, 2025.

[3] U.S. Food & Drug Administration. https://www.fda.gov/about-fda/what-we-do. Accessed July 14, 2025.

[4] National Comprehensive National Cancer Network. https://www.nccn.org/home. Accessed July 14, 2025.