# Corporate Medical Policy

# Pertuzumab, Trastuzumab, and Hyaluronidase-zzxf (Phesgo™)

**File Name:** pertuzumab_trastuzumab_hyaluronidase_phesgo
**Origination:** 10/2020
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## Description of Procedure or Service

Pertuzumab, trastuzumab, and hyaluronidase (Phesgo™) is a combination of pertuzumab and trastuzumab, HER2/neu receptor antagonists, and hyaluronidase, an endoglycosidase, indicated for the following:

- Use in combination with chemotherapy as:
  - 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 breast cancer.
  - Adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence.
- Use in combination with docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

Pertuzumab, trastuzumab, and hyaluronidase (Phesgo) was approved by the U.S. Food and Drug Administration (FDA) in June 2020 for the treatment of HER2-positive breast cancer. Pertuzumab is a recombinant humanized monoclonal antibody that targets the extracellular HER2 protein dimerization domain, inhibiting HER2 dimerization and blocking HER downstream signaling, which stops cell growth and initiates cell death. Pertuzumab binds to a different HER2 epitope than trastuzumab; thus, combining the two results in a more comprehensive blockade of HER2 and its pathways, leading to a greater treatment effect. Trastuzumab is a monoclonal antibody that binds to the extracellular HER2 domain, which mediates antibody-dependent cellular cytotoxicity by inhibiting proliferation HER2 overexpressing cells. Addition of hyaluronidase increases the absorption and dispersion rate of the subcutaneous formulation of trastuzumab.

This policy addresses pertuzumab, trastuzumab, and hyaluronidase (Phesgo). Phesgo is for subcutaneous use only in the thigh and is not administered intravenously. Phesgo has a different dosage and administration and is not interchangeable with intravenous pertuzumab (Perjeta), intravenous trastuzumab (Herceptin) and biosimilars, intravenous ado-trastuzumab emtansine (Kadcyla), or intravenous fam-trastuzumab deruxtecan (Enhertu). Pertuzumab (Perjeta), trastuzumab (Herceptin), ado-trastuzumab emtansine (Kadcyla), or fam-trastuzumab deruxtecan (Enhertu) are each addressed separately in individual policies as referenced below.

Background

Breast cancer accounts for nearly 1 in 3 cancer diagnoses in women in the U.S., and it is the most common cancer after non-melanoma skin cancer among women. After lung cancer, breast cancer ranks second for cancer mortality.

HER2-positive breast cancer is a breast cancer that tests positive for a protein called human epidermal growth factor receptor 2 (HER2), which promotes the growth of cancer cells. In the presence of too

many HER2 proteins, cancer cells are fast multiplying. Immunohisto**c**hemistry (IHC) is the test used to count the number of HER2 receptors. Cancer cells with more than two *HER2* gene copies or too many HER2 receptors are called "HER2 positive." Approximately 20-25% of breast cancers overexpress human epidermal growth factor receptor 2 (HER2), a transmembrane glycoprotein receptor with tyrosine kinase activity. Overexpression of this receptor is associated with reduced time to disease recurrence and poorer prognosis. Prior to the advent of HER2 targeted therapy, HER2 overexpression was associated with shorter disease-free and overall survival than women with either lymph node-negative or lymph node-positive breast cancers, with lack of responsiveness to tamoxifen therapy, and with altered responsiveness to cytotoxic chemotherapy.

Metastatic Breast Cancer

Metastatic breast cancer has a poor prognosis. In a cohort of 3,524 women with de novo Stage IV or relapsed breast cancer diagnosed between 1992 and 2007, the median overall survival was 39.2 months among patients with de novo Stage IV and 27.2 months among patients with relapsed disease (estimates independent of HER2 status). Factors associated with reduced survival for patients with metastatic breast cancer include age ≥50 years, visceral disease, shorter disease-free interval, negative hormone receptor status, and HER2-positive status.

Systemic treatment for metastatic breast cancer is mainly palliative. The goals of treatment are to prolong survival, alleviate symptoms, and maintain or improve quality of life. Treatment is primarily with chemotherapeutic and other anti-tumor drugs. The National Comprehensive Cancer Network (NCCN) guidelines on treatment of metastatic breast cancer include specific recommendations for first-line treatment of HER2-positive metastatic breast cancer. All recommended treatment regimens in the guidelines include trastuzumab. All of the recommended treatment regimens in the guidelines include trastuzumab. Recommended agents that are used as monotherapy or in combination with trastuzumab are paclitaxel, docetaxel, vinorelbine, capecitabine, and carboplatin.

Locally Advanced, Inflammatory and Early-stage Breast Cancer

Treatment for operable (locally invasive or early-stage) breast cancer includes surgery and/or radiotherapy followed by adjuvant chemotherapy to reduce recurrence risk. Since the advent of treatments targeting the *HER2* gene, outcomes for women with early-stage HER2-positive breast cancer have improved considerably. Among women with positive lymph nodes who are treated with chemotherapy plus trastuzumab, relapse-free survival now exceeds 80%. Current NCCN guidelines indicate that preoperative (neoadjuvant) chemotherapy may be appropriate for large tumors (>2 cm) in women with invasive breast cancer who are eligible for breast-conserving surgery. Although breast conservation rates are higher after neoadjuvant chemotherapy, a survival advantage has not been shown compared with adjuvant (postoperative) chemotherapy.

Inflammatory breast cancer is a rare, aggressive breast cancer that accounts for 1% to 6% of U.S. breast cancer cases. Inflammatory breast cancer is characterized by erythema and edema of the skin (peau d'orange) that has a palpable border and is commonly hormone receptor–negative and HER2-positive. Based on retrospective and prospective studies, current NCCN guidelines recommend preoperative chemotherapy with an anthracycline-based regimen (e.g., doxorubicin plus cyclophosphamide followed by a taxane). For patients with HER2-positive disease, NCCN recommends adding trastuzumab for up to 1 year.

**Related Medical Policies:**

Ado-Trastuzumab Emtansine (Trastuzumab-DM1) for Treatment of HER-2 Positive Malignancies
Fam-Trastuzumab Deruxtecan-nxki (Enhertu®)
Pertuzumab for Treatment of Malignancies
Trastuzumab (Herceptin®) and Trastuzumab Biosimilars

# Pertuzumab, Trastuzumab, and Hyaluronidase-zzxf (Phesgo™)

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

## Policy

**BCBSNC will provide coverage for pertuzumab, trastuzumab, and hyaluronidase-zzxf (Phesgo™) when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.**

## Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## When Pertuzumab, Trastuzumab, and Hyaluronidase-zzxf (Phesgo) is covered

**Initial Therapy**

Pertuzumab, trastuzumab, and hyaluronidase (Phesgo) may be considered medically necessary for the treatment of HER2-positive breast cancer when used for the following:

1. Neoadjuvant treatment of locally advanced, inflammatory, or early stage breast cancer (> 2cm in diameter or node-positive) as part of a complete treatment regimen for early breast cancer; **OR**
2. Adjuvant treatment of early breast cancer at high risk of recurrence; **OR**
3. Treatment of metastatic breast cancer, when used in combination with docetaxel, in patients who have not received prior anti-HER2 treatment (i.e., ado-trastuzumab emtansine, fam-trastuzumab deruxtecan, pertuzumab, trastuzumab) for metastatic disease.

Initial authorization: 12 months

**Continuation Therapy**

Continuation of treatment with pertuzumab, trastuzumab, and hyaluronidase (Phesgo) beyond 12 months after initiation of therapy, and every 12 months thereafter, is considered medically necessary for the treatment of HER2-positive breast cancer when the following criteria are met:

1. The patient is currently receiving pertuzumab, trastuzumab, and hyaluronidase (Phesgo) and continues to meet initial criteria; and
2. The patient has continued clinical benefit on pertuzumab, trastuzumab, and hyaluronidase (Phesgo) therapy as demonstrated by tumor response or lack of disease progression, and an acceptable toxicity profile.

Use of pertuzumab, trastuzumab, and hyaluronidase (Phesgo) may be considered medically necessary for clinical indications not listed above when the drug is prescribed for the treatment of cancer either:

- In accordance with FDA label (when clinical benefit has been established, (see Policy Guidelines); **OR**

- In accordance with specific strong endorsement or support by nationally recognized compendia, when such recommendation is based on strong/high levels of evidence, and/or uniform consensus of clinical appropriateness has been reached.

## When Pertuzumab, Trastuzumab, and Hyaluronidase-zzxf (Phesgo) is not covered

Pertuzumab, trastuzumab, and hyaluronidase (Phesgo) is considered **investigational** and therefore not covered when the above criteria are not met.

Pertuzumab, trastuzumab, and hyaluronidase (Phesgo) is considered investigational when used for:

1. Non-cancer indications; **OR**

2. When criteria are not met regarding FDA labeling **OR** strong endorsement/support by nationally recognized compendia, as stated under "When Pertuzumab, Trastuzumab, and Hyaluronidase-zzxf (Phesgo) is covered."

## Policy Guidelines

According to the patient selection criteria for the APHINITY trial, the trial that randomly assigned patients with node-positive or high-risk node-negative HER2-positive, operable breast cancer to receive either pertuzumab or placebo, high-risk features were defined as: histologic or nuclear grade 3, negativity for estrogen and progesterone receptors, or age younger than 35 years.

Dosing and Administration

Patients should be assessed prior to treatment initiation for HER2 protein overexpression and HER2 gene amplification using FDA-approved tests specific for breast cancer by laboratories with demonstrated proficiency. Phesgo is for subcutaneous use only in the thigh, and should not be administered intravenously. Phesgo should always be administered by a healthcare professional.

The recommended initial dose of Phesgo is 1,200 mg pertuzumab/600 mg trastuzumab/30,000 units hyaluronidase administered subcutaneously over approximately 8 minutes, followed every 3 weeks by a dose of 600 mg pertuzumab/600 mg trastuzumab/20,000 units hyaluronidase subcutaneously over approximately 5 minutes. For neoadjuvant use, administer Phesgo every 3 weeks and intravenous chemotherapy preoperatively for 3-6 cycles. For adjuvant use, administer Phesgo every 3 weeks and intravenous chemotherapy postoperatively for a total of one year (up to 18 cycles). For metastatic breast cancer, administer Phesgo subcutaneously and docetaxel intravenously every 3 weeks.

According to the manufacturer's safety information for Phesgo, administration can result in subclinical and clinical cardiac failure displayed as CHF, and decreased LVEF, with greatest risk

when given at the same time as anthracyclines. Phesgo can also cause serious and fatal pulmonary toxicity.

Evidence Summary

The efficacy of Phesgo for use in combination with chemotherapy for the treatment of patients with HER2-positive early breast cancer (neoadjuvant and adjuvant treatment) has been established using supporting evidence from adequate and well-controlled studies conducted with intravenous pertuzumab and intravenous trastuzumab in this patient population. In addition, efficacy of Phesgo for use in combination with docetaxel for treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease has also been established using supporting evidence from adequate and well-controlled studies conducted with intravenous pertuzumab and intravenous trastuzumab in this patient population. Results from a non-inferiority trial in 500 patients with operable or locally advanced (including inflammatory) HER2-positive breast cancer with a tumor size greater than 2 cm or node-positive, showed that efficacy and safety of Phesgo was comparable to intravenous pertuzumab and intravenous trastuzumab (FeDeriCa study; NCT03493854).

Drugs prescribed for treatment of cancer in accordance with FDA label may be considered medically necessary when clinical benefit has been established and should not be determined to be investigational as defined in Corporate Medical Policy (CMP), "Investigational (Experimental) Services."

Please refer to CMP "Investigational (Experimental) Services" for a summary of evidence standards from nationally recognized compendia.

## Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

*Applicable codes*: *J9316, S0353, S0354*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

Genentech, Inc. Phesgo (pertuzumab, trastuzumab, and hyaluronidase-zzxf) injection for subcutaneous use. Highlights of prescribing information. June 2020. Available at: https://www.gene.com/download/pdf/phesgo_prescribing.pdf. Last accessed September 2020.

U.S. Food and Drug Administration. FDA approves breast cancer treatment that can be administered at home by health care professional. June 29, 2020. Available at:

https://www.fda.gov/news-events/press-announcements/fda-approves-breast-cancer-treatment-can-be-administered-home-health-care-professional. Last accessed September 2020.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Breast Cancer, version 6.2020. Revised September 8, 2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Last accessed September 2020.

Medical Director review 9/2020

## Policy Implementation/Update Information

10/1/20 New policy developed. Phesgo is considered medically necessary for the treatment of HER2-positive breast cancer when specified medical criteria and guidelines are met. Added HCPCS codes C9399, J3490, J3590, J9999, S0353, and S0354 to Billing/Coding section. References added. Medical Director review 9/2020. **Policy notification given 10/1/2020 for effective date 1/1/2021**. (krc)

12/31/20 Added HCPCS code J9316 to Billing/Coding section effective 1/1/2021 and deleted C9399, J3490, J3590, and J9999 termed 12/31/2020. (krc)