Medical Drug Clinical Criteria

Subject:	Phesgo (pertuzumab/trastuzumab/hyaluronidase-zzxf)		
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Overview

This document addresses the use of Phesgo (pertuzumab/trastuzumab/hyaluronidase-zzxf). Phesgo is a combination of pertuzumab and trastuzumab, HER2/neu receptor antagonists, and hyaluronidase, an endoglycosidase, indicated for the following FDA approved indications:

Early Breast Cancer (EBC)

For use in combination with chemotherapy for:

- the neoadjuvant treatment of adult 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
- the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence

Metastatic Breast Cancer (MBC)

For use in combination with docetaxel for the treatment of adult patients

- with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease

The National Comprehensive Cancer Network® (NCCN) provides additional recommendations with a category 2A level of evidence for Phesgo which includes its use in breast cancer in invasive or inflammatory types.

Phesgo is for subcutaneous use only in the thigh. It should not be administered intravenously. Also Phesgo has different dosage and administration instructions than intravenous pertuzumab, intravenous trastuzumab, and subcutaneous trastuzumab when administered alone. Phesgo cannot be substituted for or with pertuzumab, trastuzumab, ado-trastuzumab emtansine (Kadcyla), or fam-trastuzumab deruxtecan (Enhertu). Phesgo must always be administered by a healthcare professional.

The recommended initial dose of Phesgo is 1,200 mg pertuzumab, 600 mg trastuzumab, and 30,000 units hyaluronidase administered SC over approximately 8 minutes, followed every 3 weeks by a dose of 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase administered SC over approximately 5 minutes.

- In the neoadjuvant treatment setting, Phesgo should be administered for 3 to 6 cycles as part of a treatment regimen for early breast cancer. Following surgery, patients should continue to receive Phesgo to complete 1 year of treatment (up to 18 cycles) or until disease recurrence or unmanageable toxicity, whichever occurs first, as a part of a complete regimen for early breast cancer.
- In the adjuvant treatment setting, Phesgo should be administered for a total of 1 year (up to 18 cycles) or until disease recurrence or unmanageable toxicity, whichever occurs first, as part of a complete regimen for early breast cancer, including standard anthracycline- and/or taxane-based chemotherapy. Phesgo should be started on day 1 of the first taxane containing cycle.
- In the metastatic setting, Phesgo should be administered until disease progression or unmanageable toxicity, whichever occurs first.

Black Box Warning

Phesgo has black box warnings for cardiomyopathy, embryo-fetal toxicity, and pulmonary toxicity. Phesgo administration can result in subclinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue Phesgo for cardiomyopathy. Exposure to Phesgo can result in embryo-fetal death and birth defects. Discontinue Phesgo for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome.

Definitions and Measures

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

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 ≥ 6.0 signals/cell*
    - Dual-probe HER2/CEP 17 ratio ≥ 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 < 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 ≤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 ≤ 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.

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.

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.

Phesgo (pertuzumab/trastuzumab/hyaluronidase-zzxf)

Requests for Phesgo (pertuzumab/trastuzumab/hyaluronidase-zzxf) may be approved if the following criteria are met:

I. Individual has a diagnosis of HER2-positive (HER2+) breast cancer confirmed by *one* of the following:
    A. Immunohistochemistry (IHC) is 3 +; **OR**
    B. In situ hybridization (ISH) positive;

    AND

    C. **One of the following:**
        1. Individual is using as neoadjuvant treatment; **AND**
        2. Individual is using in combination with chemotherapy; **AND**
        3. Individual has a diagnosis of 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;

        OR

        4. Individual is using as adjuvant treatment; **AND**
        5. Individual is using in combination with chemotherapy; **AND**
        6. Individual has a diagnosis of early breast cancer at high risk of recurrence;

OR

7. Individual is using for the treatment of metastatic breast cancer; **AND**
8. Individual has not received prior anti-HER2 therapy or chemotherapy for metastatic disease; **AND**
9. Individual is using in one of the following ways:
    a. Phesgo in combination with docetaxel; **OR**
    b. Phesgo alone after discontinuing combination therapy with docetaxel and continues with Phesgo until disease progression (Swain 2015);

OR

II. Individual is using Phesgo as a substitute anywhere that the combination of intravenous pertuzumab and intravenous trastuzumab (or trastuzumab biosimilars) are given as part of systemic therapy (NCCN 2A).

Requests for Phesgo (pertuzumab/trastuzumab/hyaluronidase-zzxf) may not be approved when the above criteria are not met and for all other indications.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J9316	Injection, pertuzumab, trastuzumab, and hyaluronidase-zzxf, per 10 mg [Phesgo]

ICD-10 Diagnosis

C50.011-C50.929	Malignant neoplasm of breast

Document History

Reviewed: 05/16/2025
Document History:

- 05/16/2025- Annual Review: Add clarification for use of trastuzumab biosimilars in existing criteria. Coding Reviewed: No changes.
- 05/17/2024 – Annual Review: No Changes. Coding Reviewed: No changes.
- 05/19/2023 – Annual Review: Wording and formatting updates. Coding Reviewed: No changes.
- 05/19/2023 – Annual Review: Wording and formatting updates. Coding Reviewed: No changes.
- 05/20/2022 – Annual Review: Wording and formatting updates. Coding Reviewed: No changes.
- 08/20/2021 - Annual Review: Update Phesgo criteria and quantity limits for clarification for FDA and NCCN uses. Add monotherapy use of Phesgo after combination use with docetaxel in metastatic HER 2 positive breast cancer. Coding reviewed: No changes.
- 08/21/2020– Annual Review: New criteria document for Phesgo. Coding Reviewed: Added ICD-10-CM:All dx pend, HCPCS J3490, J3590, J9999, C9399. Effective 1/1/21 Added HCPCS J9316. Effective 12/31/2020 Removed J3490, J3590, J9999, C9399. Added ICD-10-CM C50.0-C50.8. Effective 2/1/2021 extended ICD-10-CM code range to C50.011-C50.929

References

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2024. URL: http://www.clinicalpharmacology.com. Updated periodically.
2. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Updated periodically.
3. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
4. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2024; Updated periodically.
5. NCCN Clinical Practice Guidelines in Oncology™. © 2024 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on March 21, 2024.
    a. Breast Cancer. V2.2024. Revised March 11, 2024.
6. Phesgo (pertuzumab, trastuzumab, and hyaluronidase-zzxf) injection for subcutaneous use. [Package Insert]. South San Francisco, CA. Genentech; June, 2020.
7. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015;372(8):724-734. doi:10.1056/NEJMoa1413513 Available at: https://www.nejm.org/doi/pdf/10.1056/NEJMoa1413513?articleTools=true.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.