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Reviewed: 03/13/24

Revised: 04/15/24

Next Review: 03/11/25

Subject: Pertuzumab; Trastuzumab; Hyaluronidase-zzxf (Phesgo)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Pertuzumab is a monoclonal antibody that antagonizes human epidermal growth factor receptor 2 protein (HER2). As a result, pertuzumab inhibits intracellular signaling through two major signal pathways. Inhibition of these signaling pathways can result in cell growth arrest and apoptosis. In addition, pertuzumab mediates antibody-dependent cell-mediated cytotoxicity (ADCC). While pertuzumab alone inhibits the proliferation of human tumor cells, the combination of pertuzumab and trastuzumab (Herceptin®) significantly increases anti-tumor activity in HER2-overexpressing tumors. Pertuzumab and trastuzumab bind to different epitopes of HER2 receptor and have complementary mechanisms of action.

In July 2020, the FDA approved Phesgo, a combination of Perjeta (pertuzumab) and Herceptin (trastuzumab) plus hyaluronidase that is administered as a subcutaneous injection into the thigh over 5 minutes. Phesgo is approved for use in combination with chemotherapy for the following indications:

- 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.
- as adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence
- for 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.

Phesgo can be given by a healthcare professional in a treatment center or at a patient's home and the potential to eliminate a long infusion period with its shorter subcutaneous injection.

National Comprehensive Cancer Network (NCCN) Guidelines for Breast Cancer (Version 1.2024) state that Phesgo may be substituted anywhere that the combination of intravenous pertuzumab and intravenous trastuzumab are given as part of systemic therapy.

POSITION STATEMENT:

Initiation of pertuzumab, trastuzumab, and hyaluronidase-zzxf (Phesgo) **meets the definition of medical necessity** for members diagnosed with **ANY** of the following conditions when ALL associated criteria is met:

1. Breast Cancer
    a. Member has HER2-positive disease defined as **ONE** of the following:
        i. Immunohistochemistry (IHC) is 3+
        ii. Dual-probe ISH assay results:
            1. HER2/CEP17 ratio ≥2.0 **AND** average HER2 copy number ≥ 4.0 signals/cell
        iii. Concurrent dual-probe ISH assay and IHC results:
            1. HER2/CEP17 ratio ≥2.0 **AND** average HER2 copy number <4.0 signals/cell and concurrent IHC 3+
            2. HER2/CEP17 ratio <2.0 **AND** average HER2 copy number ≥6.0 signals/cell and concurrent IHC 2+ or 3+
            3. HER2/CEP17 ratio <2.0 **AND** average HER2 copy number ≥4.0 and <6.0 signals/cell and concurrent IHC 3+
    b. Use will be for **ANY** of the following:
        i. Neoadjuvant therapy
        ii. Adjuvant therapy
        iii. Metastatic (stage IV) or recurrent disease therapy
    c. Dose does not exceed **EITHER** of the following:
        i. Initial: 1,200 mg pertuzumab, 600 mg trastuzumab, and 30,000 units hyaluronidase administered subcutaneously x 1 dose
        ii. Maintenance: 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase every three weeks
2. Other FDA-approved or NCCN supported diagnosis (not previously listed above)
    a. Member meets **ONE** of the following:
        i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)

ii. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

b. Dose does not exceed either of the following:

i. Initial: 1,200 mg pertuzumab, 600 mg trastuzumab, and 30,000 units hyaluronidase administered subcutaneously x 1 dose

ii. Maintenance: 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase every three weeks

Approval duration: 6 months

Continuation pertuzumab, trastuzumab, and hyaluronidase-zzxf (Phesgo) **meets the definition of medical necessity** when **BOTH** of the following criteria are met:

1. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for treatment of breast cancer or other FDA-approved or NCCN supported diagnosis, **OR** the member has previously met all indication-specific criteria.
2. Dose not exceed 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase every three weeks

Approval duration: 6 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- For subcutaneous use in the thigh only.
- 1,200 mg pertuzumab, 600 mg trastuzumab, and 30,000 units hyaluronidase administered subcutaneously over approximately 8 minutes, followed every 3 weeks by a dose of 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase administered subcutaneously over approximately 5 minutes.
- Neoadjuvant: subcutaneous injection every 3 weeks and chemotherapy by intravenous infusion preoperatively for 3 to 6 cycles.
- Adjuvant: subcutaneous injection every 3 weeks and chemotherapy by intravenous infusion postoperatively for a total of 1 year (up to 18 cycles).
- MBC: subcutaneous injection and docetaxel by intravenous infusion every 3 weeks. (2.2)

Dose Adjustments

- See FDA approved product labeling

Drug Availability

- 1,200 mg pertuzumab, 600 mg trastuzumab, and 30,000 units hyaluronidase/15 mL (80 mg, 40 mg, and 2,000 units/mL) of solution in a single-dose vial.
- 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase/10 mL (60 mg, 60 mg, and 2,000 units/mL) of solution in a single-dose vial.

PRECAUTIONS:

Boxed Warning

- Cardiomyopathy: Administration can result in subclinical and clinical cardiac failure. The incidence and severity was highest in patients receiving anthracycline-containing chemotherapy regimens. Evaluate cardiac function prior to and during treatment. Discontinue treatment in patients receiving adjuvant therapy and withhold in patients with metastatic disease for clinically significant decrease in left ventricular function.
- Embryo-fetal Toxicity: Exposure can result in embryo-fetal death and birth defects, including oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise patients of these risks and the need for effective contraception.
- Pulmonary Toxicity: Administration can result in serious and fatal pulmonary toxicity. Discontinue PHESGO for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. Monitor patients until symptoms completely resolve.

Contraindications

- Known hypersensitivity to pertuzumab, or trastuzumab, or hyaluronidase, or to any of its excipients

Precautions/Warnings

- Exacerbation of Chemotherapy-Induced Neutropenia.
- Hypersensitivity and Administration-Related Reactions (ARRs): Monitor patients for systemic hypersensitivity reactions.

BILLING/CODING INFORMATION:

HCPCS Coding

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

ICD-10 Diagnosis Codes That Support Medical Necessity

C50.011 – C50.929	Malignant neoplasm of female and male breast

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

Adjuvant Treatment: Additional cancer treatment given after the primary treatment to lower the risk that the cancer will return. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biologic therapy. Adjuvant therapy can be used after or in combination with another form of cancer therapy and is commonly used following removal of a cancerous tumor to further help in treatment.

Metastatic cancer: when cancer spreads from the primary site (place where it started) to other places in the body.

Neo-adjuvant treatment: Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy. It is a type of induction therapy.

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

1. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2024 [cited 2/24/24]. Available from: http://www.clinicalpharmacology.com/.
2. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29 - [cited 2/24/24]. Available from: http://clinicaltrials.gov/.
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4. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2/24/24]. Available from: http://www.thomsonhc.com/.
5. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2023 [cited 2/24/24]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 03/13/23.

GUIDELINE UPDATE INFORMATION:

09/15/20	New Medical Coverage Guideline.
01/01/21	Revision: Added HCPCS code J9316 and deleted code J9999.
04/15/23	Review and revision to guidelines; updated references.
04/15/24	Review and revision to guidelines; updated references.