Effective November 1, 2018, refer to Palmetto Article A56141

BlueCross BlueShield of Alabama

"Unless otherwise noted, coverage for specific indications is effective the date of the FDA approval of that indication."
"Please check Approved by Governing Bodies for FDA approval date."

Name of Blue Advantage Policy:
Perjeta® (pertuzumab)

Policy #:	661	Effective Date:	September 30, 2016
Category:	Pharmacy	Latest Review Date:	August 2017

Background:
Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

Perjeta® (pertuzumab) is a monoclonal antibody that is a human epidermal growth factor receptor 2 (*HER2*) antagonist. Pertuzumab inhibits the HER2 signaling pathways which can result in the arrest of tumor cell growth as well as cell death. Pertuzumab also mediates antibody-dependent cell-mediated cytotoxicity (ADCC). As a single agent, pertuzumab inhibited the growth of human tumor cells, while the combination of pertuzumab and trastuzumab had complementary mechanisms of action and resulted in enhanced antitumor activity.

Perjeta® (pertuzumab) is approved by the U.S. Food and Drug Administration (FDA) in combination with trastuzumab and docetaxel as neoadjuvant treatment for individuals 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 combination of two *HER2*-active agents targeting different subdomains of *HER2* (pertuzumab targets subdomain II and trastuzumab targets subdomain IV) may result in a more comprehensive blockade of *HER2* protein and its pathways, and thus may lead to greater treatment effect.

Description of Disease

Breast cancer accounts for nearly 1 in 3 cancer diagnoses in women in the United States. Among women, breast cancer is the second most common cancer after non–melanoma skin cancer and ranks second for cancer mortality after lung cancer. In 2017, an estimated 252,710 new cases of breast cancer will be diagnosed among women, and approximately 40,610 women are expected to die from breast cancer.

Policy:

Effective for dates of service on or after November 1, 2018 refer to Palmetto Article A56141

Effective for dates of service on or after September 30, 2016 and prior to November 1, 2018:

Blue Advantage will treat **Perjeta® (pertuzumab)** as a **covered benefit** for treatment of individuals who meet Criteria (A) **AND either** (B) **OR** (C) **OR (D)** as follows:

A. The breast tumor is HER2-positve (HER2+) as documented by **one** of the following:
    1. Immunohistochemistry (IHC) is 3+; **or**
    2. In situ hybridization (ISH) positive by **any** of the following:
        a. Single probe average HER2 copy number greater than or equal to 6.0 signals/cell; **or**
        b. Dual-probe HER2/CEP 17 ratio greater than or equal to 2.0; **or**
        c. Dual-probe HER2/CEP 17 ratio less than 2.0 with an average HER2 copy number greater than or equal to 6.0 signals/cell;

AND

B. The individual has metastatic breast cancer and **both** of the following:

1. Pertuzumab will be used in combination **with** trastuzumab and **either** docetaxel* or paclitaxel*, **and**
2. The combination chemotherapy with pertuzumab will be used as single-line anti-HER2 chemotherapy for metastatic disease until progression.

*__Note__: If docetaxel or paclitaxel treatment is discontinued (for example, related to toxicity), treatment with pertuzumab and trastuzumab may continue.

OR

C. The individual has operable early stage, locally advanced, or inflammatory breast cancer and will undergo neoadjuvant (prior to surgery) therapy and **all** of the following are met:
   1. Primary tumor is larger than 2 cm in diameter or individual is node positive (clinically evident by palpation or imaging); **and**
   2. ECOG performance status 0-2; **and**
   3. Used in combination therapy **with** trastuzumab and **one** of the following:
      a. Docetaxel with or without carboplatin; **or**
      b. Paclitaxel; **and**
   4. Not continued post-operatively (adjuvant).

OR

D. The individual has **early stage or locally advanced breast cancer** and will undergo adjuvant systemic therapy and **all** of the following are met:
   1. Pertuzumab used for a maximum of 6 cycles; **and**
   2. Pertuzumab was not used as neoadjuvant therapy; **and**
   3. Primary tumor measures 2 cm or more in diameter **or** individual lymph node positive; **and**
   4. Used in combination with 12 months (52 weeks) course of trastuzumab and **one** of the following
      a. Docetaxel with or without carboplatin; or
      b. Paclitaxel

Blue Advantage will treat **Perjeta® (pertuzumab)** as a **non-covered benefit** and as **investigational** for treatment of individuals who do not meet the criteria listed above.

Blue Advantage will treat **Perjeta® (pertuzumab)** as a **non-covered benefit** and as **investigational** if it is administered after trastuzumab is discontinued or as part of a regimen without trastuzumab.

Blue Advantage will treat **Concomitant use of pertuzumab with other targeted biologic agents not otherwise noted in the criteria above**, including but not limited to erlotinib, cetuximab, panitumumab, bevacizumab, lapatinib, and ziv-aflibercept) as a **non-covered benefit** and as **investigational.**

Effective for dates of service September 1, 2015 to September 29, 2016

Blue Advantage will treat **Perjeta® (pertuzumab)** as a **covered benefit** for treatment of individuals who meet Criteria (A) **AND either** (B), OR (C) as follows:

A. The breast tumor is HER2-positve (HER2+) as documented by **one** of the following:
    a. Immunohistochemistry (IHC) is 3+; **or**
    b. In situ hybridization (ISH) positive by **any** of the following:
        i. Single probe average HER2 copy number greater than or equal to 6.0 signals/cell; **or**
        b. Dual-probe HER2/CEP 17 ratio greater than or equal to 2.0; **or**
        c. Dual-probe HER2/CEP 17 ratio less than 2.0 with an average HER2 copy number greater than or equal to 6.0 signals/cell;

AND

B. The individual has **metastatic breast cancer** and **both** of the following:
    a. Pertuzumab will be used in combination **with** trastuzumab and **either** docetaxel* or paclitaxel*, **and**
    b. The combination chemotherapy with pertuzumab will be used as single-line anti-HER2 chemotherapy for metastatic disease until progression.
    ***Note**: If docetaxel or paclitaxel treatment is discontinued (for example, related to toxicity), treatment with pertuzumab and trastuzumab may continue.

OR

C. The individual has **early stage, locally advanced, or inflammatory breast cancer** and will undergo neoadjuvant (prior to surgery) therapy and **all** of the following are met:
    a. Primary tumor is larger than 2 cm in diameter or individual is node positive (clinically evident by palpation or imaging); **and**
    b. ECOG performance status 0-2; **and**
    c. Used in combination therapy **with** trastuzumab and **one** of the following:
        b. Docetaxel with or without carboplatin; **or**
        b. Paclitaxel; **and**
    d. Not continued post-operatively (adjuvant).

Blue Advantage will treat **Perjeta® (pertuzumab)** as a **non-covered benefit** and as **investigational** for treatment of individuals who do not meet the criteria listed above.

Blue Advantage will treat **Perjeta® (pertuzumab)** as a **non-covered benefit** and as **investigational** if it is administered after trastuzumab is discontinued or as part of a regimen without trastuzumab.

Blue Advantage will treat **Concomitant use of pertuzumab with other targeted biologic agents not otherwise noted in the criteria above**, including but not limited to erlotinib, cetuximab, panitumumab, bevacizumab, lapatinib, and ziv-aflibercept) as a **non-covered benefit** and as **investigational.**

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

Neoadjuvant Therapy, Early Breast Cancer

The neoadjuvant trial entry criteria included HER2-positivity, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The phase II trial included a total of 417 participants who were randomized to one of four neoadjuvant cycles: Group A treated with trastuzumab + docetaxel; Group B treated with pertuzumab, trastuzumab + docetaxel; Group C treated with pertuzumab + trastuzumab; Group D treated with pertuzumab + docetaxel. Four cycles of neoadjuvant therapy were provided and eligible participants proceeded on to surgery. Adjuvant therapy consisted of fluorouracil, epirubicin and cyclophosphamide (FEC) except Group C which received docetaxel + FEC. A significantly improved pCR rate was observed in Group B, 45.8% (95% confidence interval [CI], 36.1-55.7) vs. 29% in Group A (95% CI, 20.6-38.5; p=0.0141). The pCR for Group C was 16.8% and Group D was 24.0%. It was also noted that in all groups, more individuals with hormone receptor-negative tumors achieved pCR with pertuzumab and trastuzumab than those individuals with hormone receptor-positive tumors. Six percent (25 of 417) of participants did not have surgery due to insufficient therapeutic response. The majority of these non-surgical candidates were from Group C. Most adverse events were grades 1-2, with the most frequently occurring events being alopecia, neutropenia, diarrhea, fatigue, rash and mucosal inflammation. The most common adverse event of grade 3 or higher was febrile neutropenia at 7-8% in Groups A, B and D. The combination of pertuzumab, trastuzumab and docetaxel significantly improved the pCR rate. Additional adjuvant trials to support the neoadjuvant approach were recommended.

Adjuvant Therapy, Early Breast Cancer

The National Comprehensive Cancer Network® (NCCN®) clinical practice guidelines (CPG) (2017) for breast cancer were updated to include an off-label 2A recommendation for the use of pertuzumab in the adjuvant setting if a regimen containing pertuzumab was not used as neoadjuvant therapy, with support based on an extrapolation of evidence from treatment (overall survival of approximately 42 months compared to 38 months in the CLEOPATRA trial) in participants with metastatic disease and improvements in pathological complete response in the neoadjuvant setting (approximately 46% for pertuzumab+, trastuzumab + docetaxel compared to 29% trastuzumab + docetaxel). In addition, specialty consensus opinion recommends the use of pertuzumab in the adjuvant setting with the identified regimens and pertuzumab is limited to a maximum of 6 cycles based on the FDA labeled dosing recommendation in the neoadjuvant setting. There is an ongoing phase III trial investigating pertuzumab as adjuvant therapy in combination with trastuzumab for HER2-positive breast cancer.

Metastatic Breast Cancer

In 2012, the FDA approved pertuzumab in combination with trastuzumab and docetaxel for individuals with HER2-positive metastatic breast cancer who have not previously received anti-HER2 therapy or chemotherapy treatment for the metastatic disease. The approval was based on the significantly improved progression-free survival (PFS) results from the phase III, double-blind, placebo-controlled Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) trial. A total of 808 participants with HER2-positive, metastatic breast cancer were enrolled into the study. Participants were eligible if they did not receive prior chemotherapy for the metastatic disease. One hormonal treatment prior to randomization was allowed. The median PFS was 18.5 months for those randomized to the group treated with pertuzumab + trastuzumab and docetaxel

compared to a median PFS of 12.4 months in the control group treated with placebo plus trastuzumab and docetaxel. The median number of treatment cycles per participant was 15 (range 1-50) in the control group and 18 (range 1-56) in the pertuzumab cohort. For both groups, the median number of cycles with docetaxel was 8; (range 1-41) for the control group and (range 1-35) for the pertuzumab group. The control group had more frequent left ventricular systolic dysfunction (8.3%) compared to the treatment group combining trastuzumab and pertuzumab (4.4%)

After an additional year of follow-up, a second interim analysis of the data from the CLEOPATRA trial was performed. Swain reported a significant survival benefit for those treated with pertuzumab compared to the placebo group. The median overall survival (OS) for the pertuzumab group was not reached (95% confidence interval [CI], 42.4 months to not estimable [NE]) compared to 37.6 months (95% CI, 34.3-NE) for the placebo cohort. The number of deaths in the placebo group compared to the pertuzumab group was statistically significant (154 of 406 [38%] vs. 113 of 402 [28%]; hazard ratio [HR] 0.66, 95% CI, 0.52-0.84; p=0.0008). The median PFS was 12.4 months (95% CI, 10.4-13.5) for the placebo group and 18.7 months (16.2-21.6) for the pertuzumab group (HR 0.69, 95% CI, 0.58-0.81). Diarrhea, rash, pruritus and mucosal inflammation occurred with higher frequencies in the pertuzumab group compared to placebo. The rate of left-ventricular systolic dysfunction was not increased in the pertuzumab cohort.

The NCCN breast cancer CPG (2017) recommends the use of pertuzumab to treat metastatic HER2-positive breast cancer in specific situations. The CPG recommends with a category 1 level of evidence, pertuzumab plus trastuzumab in combination with a taxane docetaxel as a preferred option for first-line treatment of individuals with HER2-positive metastatic breast cancer. Pertuzumab plus trastuzumab in combination with paclitaxel is an NCCN category 2A recommendation. Additionally, NCCN recommends "for patients with disease progression after treatment with trastuzumab-based therapy without pertuzumab, a line of therapy containing both trastuzumab plus pertuzumab with or without a cytotoxic agent (such as vinorelbine or taxane) may be considered." Also, specialty consensus opinion suggests that pertuzumab in combination with trastuzumab and docetaxel or paclitaxel may be used in a single line of therapy for metastatic disease.

The American Society of Clinical Oncology (ASCO) Clinical Practice Guideline for systemic therapy for treatment of advanced HER2+ breast cancer includes a strong recommendation: "Clinicians should recommend the combination of trastuzumab, pertuzumab, and a taxane for first-line treatment, unless the patient has a contraindication to taxanes." In addition, the guideline notes "Use of paclitaxel with pertuzumab and trastuzumab was also reasonable, particularly for patients who might not be good candidates for docetaxel."

HER2 Overexpression

Approximately 20% to 25% of breast cancers overexpress HER2, a transmembrane glycoprotein receptor with tyrosine kinase activity. HER2, previously called HER2/neu, or ErbB-2, belongs to the HER family of transmembrane tyrosine kinase receptors (HER1 [EGFR], HER2, HER3,

HER4). These receptors mediate tumor cell growth, survival, and differentiation. HER receptors, when activated by extracellular ligand binding, dimerize and activate cell signaling through the phosphatidyl inositol-3 (PI3)-kinase/AKT pathway, which regulates tumor cell survival, and the mitogen-activated protein kinase (MAPK) pathway, which regulates cellular proliferation. HER2 has no known ligand; it forms active heterodimers (particularly HER2:HER3) and, when overexpressed, homodimers (HER2:HER2) that constitutively activate tyrosine kinase signaling.

HER2 overexpression is associated with reduced time to disease recurrence and poorer prognosis. Before the advent of HER2-targeted therapy, HER2 overexpression was associated with shorter disease-free and OS than HER2-negative lymph node–negative or lymph node–positive breast cancers; with lack of responsiveness to tamoxifen therapy; and with altered responsiveness to cytotoxic chemotherapy.

The key selection criterion for pertuzumab and trastuzumab is HER2 overexpression. In the pivotal breast cancer clinical trials, HER2 overexpression was determined by scores of 2+ or 3+ resulting from the IHC Clinical Trial Assay (CTA), which is utilized in research settings. Individuals with scores of 0 or 1+ were not included in the trials. However, studies have shown that HER2 positivity may vary from laboratory to laboratory, and according to whether IHC or FISH methodology is used. In 2007, the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) developed joint guideline recommendations for HER2 testing in breast cancer and the guideline was updated in 2013. The guideline was established to promote complete and standardized reporting of malignant pathology to "Improve the accuracy of HER2 testing and its utility as a predictive marker in invasive breast cancer." The guideline recommends all individuals with newly diagnosed and recurrent invasive breast cancer should have tumors HER2 tested by laboratories that are accredited to perform HER2 testing. The updated guideline defines the results of HER2 testing as follows:

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

For individuals with equivocal results, the guidelines recommend additional testing with a reflex test (on the same specimen using the alternative test) or a new test (new specimen if available, using same or alternative test).

NCCN guidelines for breast cancer (2017) have incorporated the updated ASCO/CAP recommendations for HER2 status into the treatment algorithms for HER2 targeted therapy.

Other Uses
Multiple phase 2 clinical trials are currently investigating the use of pertuzumab as a treatment for other solid tumors (for example, colorectal cancer, gastric cancer, neuroendocrine tumors, non-small cell lung cancer, and prostate cancer) and in combination with other drugs and targeted therapies. However, the data demonstrating safety and efficacy from these trials have not been published.

As a result of clinical trials demonstrating the effectiveness of pertuzumab with chemotherapy, additional clinical trials are studying the efficacy of adding pertuzumab to specific targeted biologic agents and/or with other chemotherapy agents. However, at this time, there is no evidence to support the safety and efficacy of combining pertuzumab with other biologic agents not discussed above.

Additionally, investigators continue to study the prevalence and role of anti-HER2 therapy in other malignancies. However, there have been no large randomized controlled trials to draw reasonable conclusions regarding the safety and efficacy of pertuzumab versus current standard therapies for malignancies other than breast cancers.

Key Words:
Metastatic breast cancer, *HER2*-positive, neoadjuvant breast cancer treatment, Perjeta, pertuzumab

Approved by Governing Bodies:

In June 2012, pertuzumab (Perjeta®) was approved by the U.S. Food and Drug Administration (FDA) for metastatic breast cancer. Labeled indications are for "use in combination with trastuzumab and docetaxel for treatment of patients with HER2 [human epidermal growth factor receptor 2]–positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease."

In September 2013, pertuzumab was granted accelerated approval by FDA for neoadjuvant treatment of breast cancer. Labeled indications are for "use in combination with trastuzumab and docetaxel in patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer (either >2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer. This indication is based on demonstration of an improvement in pathologic complete response rate. No data are available demonstrating improvement in event-free survival or OS [overall survival]. Limitations of use:

- The safety of pertuzumab as part of a doxorubicin-containing regimen has not been established.
- The safety of pertuzumab administered for greater than 6 cycles for early breast cancer has not been established."

Data from the phase 3 APHINITY trial (expected in 2023) are required to convert accelerated approval for this indication to full approval.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:

HCPCS Codes

J9306 Injection, pertuzumab, 1 mg **(effective 01/01/2014)**

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Policy History:

Medical Policy Group, May 2016
Medical Policy Group, August 2016
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