09-J1000-75

Original Effective Date: 09/15/12

Reviewed: 03/12/25

Revised: 04/15/25

Subject: Pertuzumab (Perjeta™) Injection

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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.

Pertuzumab was initially granted approval for the treatment of HER-2 positive metastatic breast cancer in combination with trastuzumab (Herceptin®) and docetaxel (Taxol®). In September 2013, the approval was expanded to include treatment in the neoadjuvant setting. Similar to use in the metastatic setting, pertuzumab should be used in combination with trastuzumab and docetaxel.

National Comprehensive Cancer Network guidelines for Biliary Tract Cancers (Version 3.2023), Breast Cancer (Version 1.2024), Central Nervous System Cancer (Version 1.2023), Rectal Cancer (Version 1.2024), and Colon Cancer (Version 1.2024) recommend use of pertuzumab.

POSITION STATEMENT:

Initiation of pertuzumab (Perjeta™) **meets the definition of medical necessity** for members diagnosed with **ANY** of the following conditions when ALL associated criteria are met:

1. Biliary Tract Cancers: Gallbladder Cancer, Intrahepatic Cholangiocarcinoma, Extrahepatic Cholangiocarcinoma
    a. Member has been diagnosed with unresectable or resected gross residual (R2) disease, or metastatic disease
    b. 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+
    c. Pertuzumab will be used in combination trastuzumab (Herceptin)
    d. Dose does not exceed EITHER of the following:
        i. Initial: 840 mg x 1 dose
        ii. Maintenance: 420 mg every 21 days
2. Breast Cancer
    a. Member has been diagnosed with **ONE** of the following:
        i. Locally advanced, inflammatory, or early stage breast cancer
        ii. Metastatic breast cancer
        iii. Recurrent breast cancer
    b. 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+

c. Pertuzumab will be used in combination trastuzumab (Herceptin) with or without chemotherapy

d. Dose does not exceed **EITHER** of the following:

i. Initial: 840 mg x 1 dose

ii. Maintenance: 420 mg every 21 days

3. Central Nervous System Cancers

a. Member has limited or extensive brain metastases

b. Member has HER2-positive breast cancer 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+

c. Dose does not exceed EITHER of the following:

i. Initial: 840 mg x 1 dose

ii. Maintenance: 420 mg every 21 days

4. Colon Cancer

a. Member has HER2-amplified and RAS and BRAF-wildtype disease

b. Pertuzumab will be used in combination with trastuzumab (Herceptin)

c. Dose does not exceed **EITHER** of the following:

i. Initial: 840 mg x 1 dose

ii. Maintenance: 420 mg every 21 days

5. Rectal Cancer

a. Member has HER2-amplified and RAS and BRAF-wildtype disease

b. Pertuzumab will be used in combination with trastuzumab (Herceptin)

c. Dose does not exceed **EITHER** of the following:

i. Initial: 840 mg x 1 dose

ii. Maintenance: 420 mg every 21 days

6. Salivary Gland Tumors
    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. Member's disease is recurrent
    c. Pertuzumab will be used in combination with trastuzumab (Herceptin)
    d. Dose does not exceed **EITHER** of the following:
        i. Initial: 840 mg x 1 dose
        ii. Maintenance: 420 mg every 21 days
7. 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: 840 mg x 1 dose
        ii. Maintenance: 420 mg every 21 days

Approval duration: 6 months

Continuation of pertuzumab (Perjeta™) **meets the definition of medical necessity** for when **ALL** 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 biliary tract cancer, breast cancer, colon cancer,

rectal cancer, salivary gland tumor, or other FDA-approved or NCCN supported diagnosis, **OR** the member has previously met all indication-specific initiation criteria

2. Dose does not exceed 420 mg every 21 days

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 indications

Pertuzumab is FDA-approved for the following indications:

1. Treatment of HER2-positive metastatic breast cancer (MBC) in persons who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease when used in combination with trastuzumab and docetaxel
2. Neoadjuvant treatment ofHER2-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 when used in combination with trastuzumab and docetaxel

Pertuzumab should be administered as an intravenous (IV) infusion. The initial dose is 840 mg IV over 60 minutes, followed by 420 mg IV every three weeks over 30-60 minutes.

Dose Modification

Withhold pertuzumab (and trastuzumab) dose for 3 weeks or more for either of the following

1. A drop in left-ventricular ejection fraction (LVEF) to less than 45%
2. LVEF of 45%-49% with a 10% or greater absolute decrease below pretreatment values

Pertuzumab may be resumed if the LVEF has recovered to greater than 49% or to 45% to 49% associated with less than a 10% absolute decrease below pretreatment values. If after a repeat assessment within approximately 3 weeks, the LVEF has not improved, or has declined further, pertuzumab and trastuzumab should be discontinued, unless the benefits for the individual patient are deemed to outweigh the risks

Drug availability: pertuzumab is supplied as a 420 mg/14 mL single-use vial

PRECAUTIONS:

BOXED WARNING

1. Cardiomyopathy: pertuzumab can result in subclinical and clinical cardiac failure manifesting as CHF and decreased LVEF. Evaluate cardiac function prior to and during therapy. Please refer to dosage/administration section for dose modifications for confirmed decreases in LVEF.
2. Embryo-fetal toxicity: exposure to pertuzumab can result in embryo-fetal death and birth defects.

WARNINGS/PRECAUTIONS

1. Infusion-Related Reactions: Monitor for signs and symptoms. If a significant infusion-associated reaction occurs, slow or interrupt the infusion and administer appropriate medical therapies.
2. Hypersensitivity Reactions/Anaphylaxis: Monitor for signs and symptoms. If a severe hypersensitivity reaction/anaphylaxis occurs, discontinue the infusion immediately and administer appropriate medical therapies.

BILLING/CODING INFORMATION:

HCPCS Coding

J9306	Injection, pertuzumab, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

C06.9	Malignant neoplasm of mouth, unspecified
C07	Malignant neoplasm of parotid gland
C08.0-C08.9	Malignant neoplasm of other and unspecified major salivary glands
C16.0 – C16.9	Malignant neoplasm of stomach
C17.0-C17.2	Malignant neoplasm of duodenum, jejunum, ileum
C17.8	Malignant neoplasm of overlapping sites of small intestine
C18.0 – C18.9	Malignant neoplasm of colon
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C22.1	Intrahepatic bile duct carcinoma
C23	Malignant neoplasm of gallbladder
C24.0 – C24.9	Malignant neoplasm of other and unspecified parts of biliary tract
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.019	Malignant neoplasm of nipple and areola, unspecified female breast
C50.021	Malignant neoplasm of nipple and areola, right male breast
C50.022	Malignant neoplasm of nipple and areola, left male breast
C50.029	Malignant neoplasm of nipple and areola, unspecified male breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.119	Malignant neoplasm of central portion of unspecified female breast
C50.121	Malignant neoplasm of central portion of right male breast
C50.122	Malignant neoplasm of central portion of left male breast
C50.129	Malignant neoplasm of central portion of unspecified male breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.219	Malignant neoplasm of upper-inner quadrant of unspecified female breast
C50.221	Malignant neoplasm of upper-inner quadrant of right male breast
C50.222	Malignant neoplasm of upper-inner quadrant of left male breast

C50.229	Malignant neoplasm of upper-inner quadrant of unspecified male breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.319	Malignant neoplasm of lower-inner quadrant of unspecified female breast
C50.321	Malignant neoplasm of lower-inner quadrant of right male breast
C50.322	Malignant neoplasm of lower-inner quadrant of left male breast
C50.329	Malignant neoplasm of lower-inner quadrant of unspecified male breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.419	Malignant neoplasm of upper-outer quadrant of unspecified female breast
C50.421	Malignant neoplasm of upper-outer quadrant of right male breast
C50.422	Malignant neoplasm of upper-outer quadrant of left male breast
C50.429	Malignant neoplasm of upper-outer quadrant of unspecified male breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.519	Malignant neoplasm of lower-outer quadrant of unspecified female breast
C50.521	Malignant neoplasm of lower-outer quadrant of right male breast
C50.522	Malignant neoplasm of lower-outer quadrant of left male breast
C50.529	Malignant neoplasm of lower-outer quadrant of unspecified male breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.619	Malignant neoplasm of axillary tail of unspecified female breast
C50.621	Malignant neoplasm of axillary tail of right male breast
C50.622	Malignant neoplasm of axillary tail of left male breast
C50.629	Malignant neoplasm of axillary tail of unspecified male breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.819	Malignant neoplasm of overlapping sites of unspecified female breast
C50.821	Malignant neoplasm of overlapping sites of right male breast
C50.822	Malignant neoplasm of overlapping sites of left male breast
C50.829	Malignant neoplasm of overlapping sites of unspecified male breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.919	Malignant neoplasm of unspecified site 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
C78.00-C78.02	Secondary malignant neoplasm of unspecified lung
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C79.31	Secondary malignant neoplasm of brain

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

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

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.

DPD: deoxypyridinoline, also called D-Pyrilinks or Pyrilinks-D, is a crosslink of type I collagen present in bone which is excreted unmetabolized in urine and is a specific marker of bone resorption. It is measured in a urine tests in members when osteoporosis is suspected.

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

Neoadjuvant 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:

Ado-trastuzumab emtansine (Kadcyla) Injection, 09-J1000-90
Docetaxel (Taxotere®) IV, 09-J0000-95
Trastuzumab (Herceptin®) Injection, 09-J0000-86

OTHER:

None.

REFERENCES:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 03/12/25.

GUIDELINE UPDATE INFORMATION:

09/15/12	New Medical Coverage Guideline.
12/15/12	Revision to guideline; consisting of adding criteria to define HER2 positive.
04/15/13	Review and revision to guideline; consisting of updating position statement to allow treatment beyond first-line, update precautions and references.
12/15/13	Revision to guideline; consisting of updating position statement.
01/01/14	Revision to guideline; consisting of code update.
04/15/14	Review and revision to guideline; consisting of revising and reformatting position statement, dosage/administration, and precautions section; updating references and related guidelines.
04/15/15	Review and revision to guideline; consisting of revising position statement, references, definitions, program exceptions
08/15/15	Revision to guideline; consisting of revision position statement, coding
09/15/15	Revision to guideline; consisting of updating coding
11/01/15	Revision: ICD-9 Codes deleted.
04/15/16	Review and revision to guideline; position statement, description, references.
07/15/16	Revision to guideline; consisting of updating position statement.
04/15/17	Review and revision to guideline; consisting of revising references, position statement, description.
12/15/17	Revision to guideline consisting of removing HER2 documentation requirement from position statement.
04/15/18	Revision to guideline; consisting of updating position statement, references.

05/15/19	Revision to guideline; consisting of updating position statement, references, coding.
02/15/20	Revision to guideline; Updated position statement.
04/15/20	Revision to guideline; Updated position statement and references.
04/15/22	Review and revision to guideline; Updated position statement and references.
05/15/22	Updated ICD10 codes.
04/15/23	Review and revision to guidelines; updated coding, references.
04/15/24	Review and revision to guidelines; updated coding, references.
04/15/25	Review and revision to guidelines; references.