Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Pertuzumab (Perjeta®)	MP-RX-FP-71-23	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B DRUG

Service Description

This document addresses the use of Pertuzumab (Perjeta®) approved by the Food and Drug Administration (FDA) for the treatment of certain patients with HER2-positive metastatic breast cancer.

Background Information

Perjeta (pertuzumab), a recombinant humanized monoclonal antibody that targets the human epidermal growth factor receptor 2 (HER2) protein. Perjeta interrupts the communication pathway involved in the growth and progression of the cancer cells in the tumor.

The FDA approved indications for Perjeta include for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

Perjeta is also FDA approved for use in combination with trastuzumab and chemotherapy for:

- The 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
- The adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence

The National Comprehensive Cancer Network (NCCN) provides additional recommendations with a category 2A level of evidence for the use of Perjeta 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 (CLEOPATRA trial) in participants with metastatic disease and improvements in pathological complete response in the neoadjuvant setting. 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 NCCN Panel notes that FDA-approved biosimilars may be substituted for trastuzumab wherever the therapy is recommended within their guidelines.

Policy Name	Policy Number	Scope
Pertuzumab (Perjeta®)	MP-RX-FP-71-23	☒ MMM MA ☒ MMM Multihealth

Perjeta has a black box warning for Left Ventricular Dysfunction and Embryo-Fetal Toxicity. Perjeta can result in subclinical and clinical cardiac failure manifesting as decreased LVEF and CHF. Exposure to Perjeta can result in embryo-fetal death and birth defects. Advise patients of these risks and the need for effective contraception.

Definitions and Measures

- Adjuvant therapy: Treatment given after the primary treatment to increase the chances of a cure; may include chemotherapy, radiation, hormone or biological therapy.
- Disease Progression: Cancer that continues to grow or spread.
- 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. NCCN guidelines for breast cancer (2019) have incorporated the updated ASCO/CAP recommendations for HER2 status into the treatment algorithms for HER2 targeted therapy.
- 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.

Policy Name	Policy Number	Scope
Pertuzumab (Perjeta®)	MP-RX-FP-71-23	☒ MMM MA ☒ MMM Multihealth

  - Dual-probe HER2/CEP17 ratio < 2.0 with an average HER2 copy number < 4.0 signals/cell.
- Hormonal therapy: Treatment that adds, blocks, or removes hormones. Agents that slow or stop the growth of certain cancers, synthetic hormones or other drugs may be given to block the body's natural hormones.

- Line of Therapy:
  - First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
  - Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.
  - Third-line therapy: Treatment given when both initial (first-line therapy) and subsequent treatment (second-line therapy) are not effective or there is disease progression.
- 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.
- Neoadjuvant therapy: 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.
- Primary refractory disease: Cancer that does not respond at the beginning of treatment; may also be called resistant disease.
- Primary treatment: The first treatment given for a disease. It is often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation. Also called first-line therapy, induction therapy, and primary therapy.
- 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.

Approved Indications

See Background Section above.

Other Uses

Multiple phase 2 clinical trials are currently evaluating the use of pertuzumab as a treatment for other solid tumors (for example, colorectal cancer, head and neck cancers, neuroendocrine tumors, non-small cell lung cancer, prostate cancer, and rectal cancer) and in combination with other drugs and targeted therapies. However, the data demonstrating safety and efficacy from these trials have not been published and only their abstracts are available (Gupta R et.al. 2020, Meric-Bernstam F, et. al. 2019, Javie M. et.al. 2021, NCT03225937).

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

Policy Name	Policy Number	Scope
Pertuzumab (Perjeta®)	MP-RX-FP-71-23	☒ MMM MA ☒ MMM Multihealth

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.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J9306	Injection, pertuzumab, 1 mg [Perjeta]

ICD-10	Description
C08.0-C08.9	Malignant neoplasm of salivary gland
C18.0-C18.9	Malignant neoplasm of colon
C24.0-C24.9	Malignant neoplasm of biliary trac
C50.011-C50.929	Malignant neoplasm of breast
C79.81	Secondary malignant neoplasm of breast
D05.00-D05.92	Carcinoma in situ of breast
Z17.0	Estrogen receptor positive status [ER+]
Z85.3	Personal history of malignant neoplasm of breast

Policy Name	Policy Number	Scope
Pertuzumab (Perjeta®)	MP-RX-FP-71-23	☒ MMM MA ☒ MMM Multihealth

Medical Necessity Guidelines

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.

Pertuzumab (Perjeta®)

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

i. Individual has a diagnosis of HER2-positive (HER2+) breast cancer (NCCN 2A); **AND**

A. Confirmed by *one* of the following:

1. Immunohistochemistry (IHC) is 3+;

OR

2. In situ hybridization (ISH) positive;

AND

B. Individual is using in one of the following ways:

1. Individual has a diagnosis of metastatic breast cancer (Label, NCCN 1, 2A); **AND**

a. Individual is using as first line in combination with trastuzumab (or trastuzumab biosimilars) and either docetaxel or paclitaxel;

OR

b. Pertuzumab may be considered for disease progression in combination with trastuzumab (or its biosimilars), with or without cytotoxic therapy (eg, vinorelbine or taxane) for one line of therapy in those previously treated with chemotherapy and trastuzumab (or its biosimilars) without pertuzumab;

OR

2. Individual has early stage, locally advanced, or inflammatory breast cancer (Label, NCCN 2A); **AND**

a. Individual will use in one of the following ways:

i. Neoadjuvant (prior to surgery) therapy;

AND

ii. The primary tumor is larger than 2 cm in diameter or individual is lymph node positive (clinically evident by palpation or imaging);

OR

iii. Adjuvant systemic therapy;

AND

iv. The cancer is at high risk of recurrence;

AND

b. Individual has a ECOG performance status of 0-2; **AND**

c. Individual is using in combination with trastuzumab (or trastuzumab biosimilars) and either of the following (label, NCCN 2A):

i. Docetaxel with or without carboplatin;

OR

ii. Paclitaxel;

AND

d. Individual is using pertuzumab for a maximum of 18 cycles (12 month course) (NCCN 2A);

OR

C. Individual is requesting Perjeta in combination with trastuzumab (or trastuzumab biosimilars) for 12 months after completing 6 cycles (18 weeks) of TCHP (docetaxel, carboplatin, trastuzumab (or trastuzumab biosimilars), pertuzumab) for early stage, locally advance, or inflammatory breast cancer (NCCN 2A);

OR

D. Individual has metastatic breast cancer with brain metastases and the following criteria are met (NCCN 2A); **AND**

1. Individual has a primary diagnosis of HER2+ breast cancer; **AND**
2. Used in one of the following ways:
   a. In those with asymptomatic brain metastases as primary or initial therapy;

   OR

   b. In those with recurrent or stable disease;

AND

3. Individual is using in combination with trastuzumab (or trastuzumab biosimilars).

OR

ii. Individual has a diagnosis of biliary tract cancer (extrahepatic cholangiocarcinoma, intrahepatic cholangiocarcinoma, or gallbladder cancer) (NCCN 2A); **AND**

A. Individual is using as subsequent treatment in combination with trastuzumab (or its biosimilars); **AND**

B. Individual is using in one of the following ways:

1. For progression on or after systemic treatment for unresectable or resected gross residual (R2) disease; **OR**
2. Metastatic disease that is HER2-positive;

OR

iii. Individual has a diagnosis of colon or rectal cancer (NCCN 2A); **AND**

A. Individual is using in one of the following ways:

1. As initial systemic therapy in combination with trastuzumab (or its biosimilars) if intensive therapy not recommended; **AND**
   a. No prior treatment with a HER2 inhibitor; **AND**
   b. One of the following:
      i. For advanced or metastatic disease proficient mismatch repair/microsatellite-stable (pMMR/MSS); **OR**

ii. Ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) and HER2-amplified and RAS and BRAF wild-type disease;

OR

2. As subsequent therapy in combination with trastuzumab (or its biosimilars); **AND**
    a. For HER2-amplified and RAS and BRAF wild-type pMMR/MSS disease; **OR**
    b. Ineligible for or progression on checkpoint inhibitor immunotherapy for dMMR/MSI-H if intensive therapy not recommended and no prior treatment with a HER2 inhibitor;

OR

3. As initial treatment in combination with trastuzumab (or its biosimilars); **AND**
    a. For HER2-amplifed and RAS and BRAF wild-type pMMR/MSS only; **AND**
    b. Has unresectable metachronous metastases disease; **AND**
    c. Prior FOLFOX or CapeOX usage within the past 12 months;

OR

iv. Individual has a diagnosis of HER2-positive recurrent salivary gland tumor (NCCN 2A); **AND**
    A. Individual is using as systemic therapy in combination with trastuzumab (or its biosimilars); **AND**
    B. With no surgery or radiation therapy option.

B. Criteria For Continuation of Therapy

i. MMM considers continuation of Pertuzumab (Perjeta®) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when there is no evidence of unacceptable toxicity or disease progression while on the current regimen, and the recommended duration of therapy has not been exceeded. The following information should be submitted for reauthorization:
    A. A current oncology note documenting the patient's response to treatment showing no progression of disease.
    B. Current imaging studies and other objective measures, as appropriate, showing no progression of disease when compared with previous results.

Policy Name	Policy Number	Scope
Pertuzumab (Perjeta®)	MP-RX-FP-71-23	☒ MMM MA ☒ MMM Multihealth

C. Authorization Duration

Use	Initial Approval Duration	Reauthorization Approval Duration	Treatment Duration
Metastatic Breast Cancer	Up to 6 months	Up to 6 months	○ Until disease progression or unmanageable toxicity.
Neoadjuvant treatment of breast cancer (prior to surgery)	As requested, up to a maximum of 12 weeks	As needed to complete a total duration of therapy of 12 weeks	○ When Perjeta is administered (preoperative) with trastuzumab or trastuzumab hyaluronidase-oysk and docetaxel: Perjeta is used for four (4) preoperative cycles (12 weeks; 3 months).
	As requested up to a maximum of 12 weeks (or 9 weeks, depending on the regimen)	N/A	○ When Perjeta is administered as neoadjuvant (preoperative) in combination with docetaxel and trastuzumab or trastuzumab hyaluronidase-oysk: Perjeta is used for 3 or 4 preoperative cycles (9-12 weeks).
	As requested up to a maximum of 18 weeks	As needed to complete a total duration of therapy of 18 weeks	○ When Perjeta is administered as neoadjuvant (preoperative) in combination with docetaxel, carboplatin, and trastuzumab (TCH) or trastuzumab hyaluronidase-oysk: Perjeta is used for 6 cycles (18 weeks; 4.5 months).
	As requested up to a maximum of 12 weeks	As needed to complete a total duration of therapy of 12 weeks	○ When Perjeta is used as neoadjuvant (preoperative) in combination with paclitaxel and trastuzumab or trastuzumab hyaluronidase-oysk [after 4 cycles of dose-dense doxorubicin and cyclophosphamide (ddAC)]: Perjeta is used for 4 cycles (12 weeks; 3 months)
Adjuvant treatment of Breast Cancer (after surgery)	Up to 6 months	As needed to complete a total duration of therapy of 1 year.	For a total of 1 year (up to 18 cycles) or until disease recurrence or unmanageable toxicity

Policy Name	Policy Number	Scope
Pertuzumab (Perjeta®)	MP-RX-FP-71-23	☒ MMM MA ☒ MMM Multihealth

D. **Conditions Not Covered**

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. If pertuzumab is administered after trastuzumab (or trastuzumab biosimilars) is discontinued or as part of a regimen without trastuzumab (or trastuzumab biosimilars)
ii. 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)
iii. When the above criteria (Section A, Criteria for Initial Approval) are not met and for all other indications.

Limits or Restrictions

A. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Policy Name	Policy Number	Scope
Pertuzumab (Perjeta®)	MP-RX-FP-71-23	☒ MMM MA ☒ MMM Multihealth

Use	Recommended Dosing Schedule
Metastatic Breast Cancer	Initial dose of 840 mg, followed by 420 mg every 3 weeks thereafter.
Neoadjuvant treatment of breast cancer (prior to surgery)	Initial dose of 840 mg, followed by 420 mg every 3 weeks for 3 to 6 weeks.
Adjuvant treatment of Breast Cancer (after surgery)* *Perjeta should be administered as part of a complete regimen for early breast cancer, including standard anthracycline- and/or taxane-based chemotherapy	Initial dose of 840 mg, followed by 420 mg every 3 weeks thereafter.

Exceptions

- Perjeta is a fixed dose, regardless of body weight. The initial dose of Perjeta is 840 mg, followed by 420 mg every 3 weeks after.
- Perjeta is always administered in regimens containing trastuzumab. Perjeta should be discontinued if trastuzumab or trastuzumab hyaluronidase-oysk treatment is discontinued.
- When using Perjeta, the dose of concomitant medications should be adjusted:
  - When administered with Perjeta, the recommended initial dose of trastuzumab is 8 mg/kg, followed every 3 weeks by a dose of 6 mg/kg administered as an intravenous infusion over 30 to 90 minutes.
  - When administered with Perjeta, the recommended initial dose of trastuzumab hyaluronidase-oysk is 600 mg/10,000 units (600 mg trastuzumab and 10,000 units hyaluronidase) once every three weeks irrespective of the patient's body weight.

Policy Name	Policy Number	Scope
Pertuzumab (Perjeta®)	MP-RX-FP-71-23	☒ MMM MA ☒ MMM Multihealth

Reference Information

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2023. 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. Accessed: January 12, 2023.
3. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
4. Evaluation of Trastuzumab in Combination With Lapatinib or Pertuzumab in Combination With Trastuzumab-Emtansine to Treat Patients With HER2-positive Metastatic Colorectal Cancer (HERACLES). https://clinicaltrials.gov/ct2/show/ NCT03225937.
5. Gupta R, Garrett-Mayer E, Halabi S, et al. Pertuzumab plus trastuzumab (P+T) in patients (Pts) with colorectal cancer (CRC) with ERBB2 amplification or overexpression: Results from the TAPUR Study [abstract]. Journal of Clinical Oncology 2020;38:132-132. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.4_suppl.132.
6. Javle M, Borad MJ, Azad NS, et al. Pertuzumab and trastuzumab for HER2-positive metastatic biliary tract cancer (MyPathway): A multicentre, open-label, phase 2a, multiple basket study. Lancet Oncol 2021;22:1290-1300.
7. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2022; Updated periodically.
8. Meric-Bernstam F, Hurwitz H, Raghav KPS, et al. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. Lancet Oncol 2019;20:518-530. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30857956.
9. NCCN Clinical Practice Guidelines in Oncology™. © 2023 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on January 12, 2023.
    a. Breast Cancer. V4.2022. Revised June 21, 2022.
    b. Central Nervous System Cancers. V2.2022. Revised September 29, 2022.
    c. Colon Cancer. V2. 2022. Revised October 27, 2022.
    d. Hepatobiliary Cancers. V4.2022. Revised December 9, 2022.
    e. Head and Neck Cancers. V1.2023. Revised December 20, 2022.
    f. Rectal Cancer. V3. 2022. Revised October 27, 2022.

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.

Policy Name	Policy Number	Scope
Pertuzumab (Perjeta®)	MP-RX-FP-71-23	☒ MMM MA ☒ MMM Multihealth

Policy History

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Annual Review	Update existing criteria for use in metastatic breast cancer following chemotherapy and trastuzumab. Clarify existing NCCN 2A criteria for breast cancer in first-line therapy and progression. Add NCCN category 2A recommendation for use in biliary tract cancers. Add NCCN category 2A criteria for use in colon or rectal cancer. Add NCCN category 2A criteria for use in salivary gland tumors. Wording and formatting updates. Coding Reviewed: Added ICD-10-CM C08.0-C08.9, C18.0-C18.9, C24.0-C24.9.	11/18/2024	12/17/2024
Select Review	Update statement for criteria for initial approval: Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met all approval criteria.	3/25/2024	5/9/2024
Policy Inception	Elevance Health's Medical Policy adoption.	N/A	11/30/2023

Revised: 10/3/2024