CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Pertuzumab (Perjeta®)

Version: 1.0

EFFECTIVE DATE: 1/1/2024

NantHealth® | Eviti®

Please note the following:

Pertuzumab (Perjeta®)

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

Note: For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Pertuzumab (Perjeta): Discussion

Pertuzumab is a monoclonal antibody that attaches to HER2 proteins on the surface of HER2-positive cancer cells and blocks the signals that cause cancer cells to multiply. It attaches to the HER2 protein in a different way from trastuzumab, so the two medicines work together well. After attaching to cancer cells, it can also alert the immune system to kill them. [1]

Pertuzumab is approved by the Food and Drug Administration (FDA) for:

- Use in combination with trastuzumab and docetaxel for treatment of HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.
- Use in combination with trastuzumab and chemotherapy as neoadjuvant treatment for 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.
- Adjuvant treatment of HER2-positive early breast cancer at high risk of recurrence. [2]

Pertuzumab can cause left ventricular dysfunction manifested as decreased left ventricular ejection fraction (LVEF) and congestive heart failure (CHF). [2]

The National Comprehensive Cancer Network (NCCN) endorses pertuzumab in the following cancer types: biliary tract cancer, breast cancer, central nervous system cancer, colon cancer, head and neck cancer, and rectal cancer. [3, 4, 5, 6, 7, 8]

Pertuzumab: Definitions

- **BRAF gene** - A gene that encodes a protein belonging to the RAF family of serine/threonine protein kinases. This protein plays a role in regulating the MAP kinase/ERK signaling pathway, which affects cell division, differentiation, and secretion.
- **BRAF wild-type** - The natural, unchanged (unmutated) form of the gene.
- **Deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H)** - When the microsatellite DNA segments in cancer cells show changes (mutations), this indicates that the tumor cells are deficient in the repair of the mismatch errors. These cancers have microsatellite instability (also called MSI-High, MSI-H, or mismatch repair deficiency, dMMR).

- **Food and Drug Administration (FDA)** - The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
- **Human Epidermal Growth Factor Receptor 2 (HER2) -** A protein involved in normal cell growth. HER2/neu may be made in larger than normal amounts by some types of cancer cells, including breast, ovarian, bladder, pancreatic, stomach, and esophageal cancers. This may cause cancer cells to grow more quickly and spread to other parts of the body.
- **National Comprehensive Cancer Network (NCCN) -** An alliance of thirty-two leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.
- **Proficient mismatch repair/microsatellite-stable (pMMR/MMS) -** When microsatellite DNA segments are unchanged (not mutated), the tumor cells are considered microsatellite stable (MSS) or have proficient mismatch repair. MSS cancers have normal levels of mismatch repair gene and protein expression and can correct DNA mismatch repair errors proficiently.
- **RAS gene** - A family of genes that make proteins involved in cell signaling pathways that control cell growth and cell death. Mutated (changed) forms of the RAS gene may be found in some types of cancer. These changes may cause cancer cells to grow and spread in the body. Members of the RAS gene family include KRAS, HRAS, and NRAS.
- **RAS wild-type** - The natural, unchanged (unmutated) form of the gene.

Pertuzumab: Policy

Pertuzumab will be considered for coverage when the following criteria are met:

Biliary Tract Cancers
(Extrahepatic and Intrahepatic Cholangiocarcinoma, Gallbladder Cancer)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Subsequent treatment in combination with trastuzumab for progression on or after systemic treatment for unresectable or resected gross residual (R2) disease, or metastatic disease that is HER2-positive [3]

Breast Cancer - Invasive

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Preoperative systemic therapy for human epidermal growth factor receptor 2 (HER2)-positive tumors and locally advanced c≥T2 or cN+ and M0 disease, or cT1c, cN0 disease as follows:
    a) In combination with one of the following:
        i. Trastuzumab and paclitaxel following adjuvant and non-adjuvant chemotherapy [(AC) (doxorubicin and cyclophosphamide)] - dose-dense or every 3 weeks
        ii. Trastuzumab and docetaxel following AC
        iii. Paclitaxel and trastuzumab

b) As a component of TCHP (docetaxel, carboplatin, trastuzumab and pertuzumab); OR

4. Adjuvant systemic therapy for human epidermal growth factor receptor 2 (HER2)-positive tumors and cT1c-3, cN0 or N+, M0 (pT1-3 and pN0 or pN+ tumors) disease as follows:
    a) In combination with one of the following:
        i. Trastuzumab and paclitaxel following AC (doxorubicin and cyclophosphamide) (dose-dense or every 3 weeks)
        ii. Trastuzumab and docetaxel following AC
        iii. Paclitaxel and trastuzumab
    b) As a component of TCHP (docetaxel, carboplatin, trastuzumab and pertuzumab); OR
5. Adjuvant systemic therapy for human epidermal growth factor receptor 2 (HER2)-positive tumors and locally advanced c≥T2 or cN+ and M0 disease, or cT1c, cN0 disease following completion of planned chemotherapy and following mastectomy or breast-conserving surgery (BCS) with surgical axillary staging, with trastuzumab for one of the following:
    a) Hormone receptor-negative and ypT0N0 or pCR
    b) Hormone receptor-positive and ypT0N0 or pCR
    c) YpT1-4N0 (if ado-trastuzumab discontinued for toxicity)
    d) YpN≥1 (if ado-trastuzumab discontinued for toxicity); OR
6. Used for recurrent unresectable (local or regional) or stage IV (M1) human epidermal growth factor receptor 2 (HER2)-positive disease that is either hormone receptor-negative or hormone receptor-positive for one of the following:
    a) First-line therapy in combination with trastuzumab with either docetaxel or paclitaxel
    b) In combination with trastuzumab with or without cytotoxic therapy (e.g., vinorelbine or taxane) for one line of therapy in those previously treated with chemotherapy and trastuzumab in the absence of pertuzumab

Notes:

1. It is acceptable to change the administration sequence to taxane (with or without HER2-targeted therapy) followed by AC.
2. If there is no residual disease after preoperative therapy or no preoperative therapy, complete up to one year of HER2 targeted therapy with trastuzumab with or without pertuzumab after completing the planned chemotherapy regimen course. If residual disease is present after preoperative therapy and ado-trastuzumab emtansine is discontinued for toxicity, then trastuzumab with or without pertuzumab to complete one year of therapy can be used.

Breast Cancer - Inflammatory

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Preoperative systemic therapy for human epidermal growth factor receptor 2 (HER2)-positive disease for one of the following:
    a) In combination with trastuzumab and paclitaxel following AC (doxorubicin and cyclophosphamide) (dose-dense or every 3 weeks) regimen
    b) As a component of TCHP (docetaxel, carboplatin, trastuzumab and pertuzumab) regimen
    c) In combination with trastuzumab and docetaxel following AC regimen
    d) In combination with paclitaxel and trastuzumab; OR

4. Adjuvant systemic therapy for those who had a response to preoperative systemic therapy, followed by surgery, and need to complete planned chemotherapy, for node-positive human epidermal growth factor receptor 2 (HER2)-positive tumors only as follows:
    a) In combination with one of the following:
        i. Trastuzumab and paclitaxel following AC (doxorubicin and cyclophosphamide) (dose-dense or every 3 weeks) regimen
        ii. Paclitaxel and trastuzumab
        iii. Trastuzumab and docetaxel following AC regimen
    b) As a component of TCHP (docetaxel, carboplatin, trastuzumab and pertuzumab) regimen; OR
5. Used for those with no response to preoperative systemic therapy, or recurrent unresectable (local or regional) or stage IV (M1) human epidermal growth factor receptor 2 (HER2) positive disease that is either hormone receptor-negative or hormone receptor-positive in combination with one of the following:
    a) First-line therapy with trastuzumab with either docetaxel or paclitaxel
    b) Trastuzumab with or without cytotoxic therapy (e.g., vinorelbine or taxane) for one line of therapy in patients previously treated with chemotherapy and trastuzumab in the absence of pertuzumab [4]

Notes:

1. It is acceptable to change the administration sequence to taxane (with or without HER2-targeted therapy) followed by AC.
2. If there is no residual disease after preoperative therapy or no preoperative therapy, complete up to one year of HER2 targeted therapy with trastuzumab with or without pertuzumab after completing the planned chemotherapy regimen course. If residual disease is present after preoperative therapy and ado-trastuzumab emtansine is discontinued for toxicity, then trastuzumab with or without pertuzumab to complete one year of therapy can be used.

Central Nervous System Cancers

Extensive Brain Metastases

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Used in combination with high-dose trastuzumab as the treatment for extensive brain metastases in HER2-positive breast cancer for one of the following:
    a) Primary treatment in select cases (E.g., small asymptomatic brain metastases)
    b) Treatment for recurrent disease with stable systemic disease or reasonable systemic treatment options

Limited Brain Metastases

1. Age 18 years or older; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Used in combination with high-dose trastuzumab as the treatment for limited brain metastases in HER2-positive breast cancer for one of the following:
    a) Initial treatment in select cases (E.g., small asymptomatic brain metastases)
    b) Treatment for recurrent brain metastases

c) Treatment of relapsed disease with either stable systemic disease or reasonable systemic treatment options [5]

Colon Cancer

1. Age 18 years or older; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Adjuvant therapy in combination with trastuzumab (HER2-amplified and RAS and BRAF wild-type) if intensive therapy is not recommended for one of the following:
    a) Treatment following resection and/or local therapy for resectable metachronous metastases in those who have received previous chemotherapy (proficient mismatch repair/microsatellite-stable (pMMR/MSS) or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H)
    b) Treatment following resection and/or local therapy for resectable metachronous metastases in those who have received previous immunotherapy (dMMR/MSI-H)
    c) Treatment for unresectable metachronous metastases that converted to resectable disease after initial treatment. Biologic therapy is only appropriate for continuation of favorable response from conversion therapy (pMMR/MSS or ineligible for or progression on checkpoint inhibitor immunotherapy for dMMR/MSI-H); OR
4. Therapy in combination with trastuzumab (HER2-amplified and RAS and BRAF wild-type) (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) if intensive therapy is not recommended and have not received previous treatment with a HER2 inhibitor for one of the following:
    a) Primary treatment for locally unresectable or medically inoperable disease
    b) Primary treatment for synchronous abdominal/peritoneal metastases that are nonobstructing, or following local therapy with existing or imminent obstruction
    c) Synchronous unresectable metastases of other sites
    d) Initial treatment for unresectable metachronous metastases in those who have not received previous FOLFOX or CapeOX within the past 12 months, who have received previous fluorouracil/leucovorin (5-FU/LV) or capecitabine therapy, or who have not received any previous chemotherapy; OR
5. Initial treatment in combination with trastuzumab (HER2-amplified and RAS and BRAF wild-type) (proficient mismatch repair/microsatellite-stable [pMMR/MSS] only) for those with unresectable metachronous metastases and previous FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months; OR
6. Subsequent therapy in combination with trastuzumab for progression of advanced or metastatic disease (HER2-amplified and RAS and BRAF wild-type) (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) not previously treated with HER2 inhibitor, for any previous therapy with one of the following:
    a) Oxaliplatin-based therapy without irinotecan
    b) Irinotecan-based therapy without oxaliplatin
    c) Oxaliplatin and irinotecan; OR
7. Subsequent therapy in combination with trastuzumab for progression of advanced or metastatic disease (HER2-amplified and RAS and BRAF wild-type) (proficient mismatch

repair/microsatellite-stable [pMMR/MSS] or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) not previously treated with HER2 inhibitor, for any previous therapy without one of the following:

a) Irinotecan or oxaliplatin
b) Irinotecan or oxaliplatin followed by FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) with or without bevacizumab

Colon Cancer - Appendiceal Adenocarcinoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Initial systemic therapy for advanced or metastatic disease (proficient mismatch repair/microsatellite-stable (pMMR/MSS) or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) (HER2-amplified and RAS and BRAF wild-type) in combination with trastuzumab if intensive therapy is not recommended and has not received previous treatment with a HER2 inhibitor; OR
4. Subsequent therapy in combination with trastuzumab for progression of advanced or metastatic disease (proficient mismatch repair/microsatellite-stable (pMMR/MSS) or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) (HER2-amplified and RAS and BRAF wild-type) and has not previously been treated with HER2 inhibitor, for any previous therapy with one of the following:
    a) Oxaliplatin-based therapy without irinotecan
    b) Irinotecan-based therapy without oxaliplatin
    c) Oxaliplatin and irinotecan
5. Subsequent therapy in combination with trastuzumab for progression of advanced or metastatic disease (proficient mismatch repair/microsatellite-stable (pMMR/MSS) or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) (HER2-amplified and RAS and BRAF wild-type) and has not previously been treated with HER2 inhibitor, for any previous therapy without one of the following:
    a) Irinotecan or oxaliplatin
    b) Irinotecan or oxaliplatin followed by FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) with or without bevacizumab [6]

Head and Neck Cancers - Salivary Gland Tumors

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. In combination with trastuzumab for human epidermal growth factor receptor 2 (HER2)-positive recurrent disease for one of the following:
    a) Distant metastases in patients with a performance status (PS) of 0-3
    b) Unresectable locoregional recurrence or second primary with prior radiation therapy [7]

Rectal Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Therapy in combination with trastuzumab (HER2-amplified and RAS and BRAF wild-type) if intensive therapy is not recommended for one of the following:
    a) Adjuvant treatment (following resection and/or local therapy) for resectable metachronous metastases in those who have received previous chemotherapy (proficient mismatch repair/microsatellite-stable [pMMR/MSS] only or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H])
    b) As adjuvant treatment (following resection and/or local therapy) for resectable metachronous metastases who have received previous immunotherapy (dMMR/MSI-H only)
    c) As adjuvant treatment for unresectable metachronous metastases that converted to resectable disease after initial treatment. Biologic therapy is only appropriate for continuation of favorable response from conversion therapy (pMMR/MSS only or ineligible for or progression on checkpoint inhibitor immunotherapy for dMMR/MSI-H); OR
4. Initial treatment in combination with trastuzumab (HER2-amplified and RAS and BRAF wild-type) with unresectable metachronous metastases (proficient mismatch repair/microsatellite-stable [pMMR/MSS] only) and previous FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months; OR
5. Primary treatment in combination with trastuzumab for T3, N Any; T1-2, N1-2; T4, N Any; or locally unresectable or medically inoperable disease (HER2-amplified and RAS and BRAF wild-type only) if resection is contraindicated following total neoadjuvant therapy (proficient mismatch repair/microsatellite-stable [pMMR/MSS] only or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) or neoadjuvant/definitive immunotherapy (dMMR/MSI-H only) if intensive therapy is not recommended; OR
6. Therapy in combination with trastuzumab (HER2-amplified and RAS and BRAF wild-type) (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) if intensive therapy is not recommended and who have not received previous treatment with a HER2 inhibitor as follows:
    a) Primary treatment for synchronous abdominal/peritoneal metastases that are nonobstructing, or following local therapy for patients with existing or imminent obstruction
    b) Primary treatment for synchronous unresectable metastases of other sites
    c) Primary treatment for unresectable isolated pelvic/anastomotic recurrence
    d) Initial treatment for unresectable metachronous metastases in those who have not received previous FOLFOX or CapeOX within the past 12 months, who have received previous fluorouracil/leucovorin (5-FU/LV) or capecitabine therapy, or who have not received any previous chemotherapy; OR
7. Subsequent therapy in combination with trastuzumab for progression of advanced or metastatic disease (HER2-amplified and RAS and BRAF wild-type) (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progression on checkpoint inhibitor

immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) who have not been previously treated with HER2 inhibitor, for any previous therapy with one of the following:
    a) Oxaliplatin-based therapy without irinotecan
    b) Irinotecan-based therapy without oxaliplatin
    c) Oxaliplatin and irinotecan; OR
8. Subsequent therapy in combination with trastuzumab for progression of advanced or metastatic disease (HER2-amplified and RAS and BRAF wild-type) (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) who have not been previously treated with HER2 inhibitor, for any previous therapy without one of the following:
    a) Irinotecan or oxaliplatin
    b) Irinotecan or oxaliplatin followed by FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) with or without bevacizumab [8]

Note: Coverage of pertuzumab will be provided for an FDA-approved indication or National Comprehensive Cancer Network (NCCN) guidelines when it is a Category 1, 2A, or 2B recommendation or when all criteria are met.

Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

Pertuzumab: References

1. Living Beyond Breast Cancer. https://www.lbbc.org/about-breast-cancer/treatments/chemotherapy/common-regimens/thp-docetaxel-trastuzumab. Accessed July 5, 2023.
2. Pertuzumab (Perjeta) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125409s124lbl.pdf. Accessed July 5, 2023.
3. National Comprehensive Cancer Network Guidelines. Biliary Tract Cancers (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf. Accessed July 5, 2023.
4. National Comprehensive Cancer Network Guidelines. Breast Cancer (Version 4.2023). https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed on July 5, 2023.
5. National Comprehensive Cancer Network Guidelines. Central Nervous System Cancers (Version 1.2023). https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed on July 5, 2023.
6. National Comprehensive Cancer Network Guidelines. Colon Cancer (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed July 6, 2023.
7. National Comprehensive Cancer Network Guidelines. Head and Neck Cancers (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed July 06, 2023.
8. National Comprehensive Cancer Network Guidelines. Rectal Cancer (Version 4.2023). https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed July 28, 2023.

Pertuzumab: Coding (CPT®, ICD 10 and HCPCS) *

*Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment. CPT codes are available through the AMA.

CODE	DESCRIPTION
C08.9	Head and Neck Cancers - Salivary Gland Tumors
C18.1	Colon Cancer - Appendiceal Adenocarcinoma
C18.9	Colon Cancer
C20.0	Rectal Cancer
C22.1	Biliary Tract Cancers - Intrahepatic Cholangiocarcinoma
C23.0	Biliary Tract Cancers - Gallbladder Cancer
C24.0	Biliary Tract Cancers - Extrahepatic Cholangiocarcinoma
C50.9	Breast Cancer
C72.9	Central Nervous System Cancers
J9036	Pertuzumab (Perjeta)

Pertuzumab: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	1/1/2024
2	Policy Review Dates:	8/4/2023
3	Policy Revision Dates:	

4	Department Owner:	Medical Affairs
5	NH Advisory Committee Approval Dates:	10/5/2023
6	Revision Changes:	