Clinical Policy: HER2 Breast Cancer Treatments
Reference Number: NE.PHAR.67
Effective Date: 01/01/2017
Last Review Date:

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
The intent of the criteria is to ensure that patients follow selection elements established by Centene® medical policy for Herceptin, Kadcyla and Perjeta.

Table 1: Indications$^{1-3,10}$

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>FDA-Approved Indication</th>
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</thead>
</table>
| **Herceptin** | trastuzumab | **HER2-Positive Breast Cancer$^1$**
|  |  | • Adjuvant treatment of HER2-overexpressing node-positive or node-negative breast cancer; if node negative, also with one of the following high-risk features: ER/PR-negative, tumor size>2 cm, age<35 years, or histologic and/or nuclear Grade 2 or 3:
|  |  | o As part of a treatment regimen containing doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
|  |  | o With docetaxel and carboplatin
|  |  | o As a single agent following multi-modality anthracycline-based therapy
|  |  | • In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer (MBC) and as a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.
|  |  | **HER2-Positive Gastric or Gastroesophageal Junction Cancer$^1$**
|  |  | • In combination with cisplatin and capecitabine or 5-fluorouracil for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease.
|  |  | **Compendial Use: HER2-Positive Esophageal Cancer (not FDA approved)$^{10}$**
|  |  | • In combination with cisplatin and capecitabine or 5-fluorouracil for the treatment of patients with HER2-overexpressing metastatic or locally advanced esophageal cancer where local therapy is not indicated and for which the patient has not received prior treatment for metastatic disease.
**CLINICAL POLICY**
**HER2 Breast Cancer Treatments**

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| Kadcyla    | ado-trastuzumab emtansine | **HER2-Positive Breast Cancer**<sup>2</sup>  
- Treatment of patients with HER2-positive, MBC who previously received trastuzumab and a taxane, separately or in combination. Patients should have either received prior therapy for metastatic disease or developed disease recurrence during or within six months of completing adjuvant therapy. |
| Perjeta    | pertuzumab           | **HER2-Positive Breast Cancer**<sup>3</sup>  
- Use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive MBC who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.  
- Use in combination with trastuzumab and docetaxel as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete [preoperative] treatment regimen for early breast cancer.  
*Limitations of Use:*  
- *The safety of PERJETA as part of a doxorubicin-containing regimen has not been established.*  
- *The safety of PERJETA administered for greater than 6 cycles for early breast cancer has not been established.* |

**Policy/Criteria**

It is the policy of health plans affiliated with Centene Corporation® that Herceptin, Kadcyla and Perjeta are **medically necessary** for members who meet the following algorithm criteria:

*Figure 1.* Herceptin Algorithm  
*Figure 2.* Kadcyla Algorithm  
*Figure 3.* Perjeta Algorithm
**Figure 1. Herceptin Algorithm**

- **HER2 positive breast cancer**
  - **What is the diagnosis?**
    - HER2 positive metastatic gastric, esophageal or gastroesophageal
      - Other
    - **Treatment of metastatic disease**
      - Received previous chemotherapy and/or anti-HER2 therapy for metastasis?
        - Yes
          - Received prior treatment for metastatic disease?
            - Yes
              - Deny
            - No
              - **Being used in combination with cisplatin and capecitabine or 5-fluorouracil?**
                - Yes
                  - Deny
                - No
                  - **Currently receiving Herceptin?**
                    - Yes
                      - Disease progression or unmanageable toxicity since starting Herceptin? (App C)
                        - Yes
                          - Approve 6 months, (max 52 weeks lifetime for adjuvant treatment)
                        - No
                          - Approve 3 months
                        - Deny
                    - No
                      - **Is Herceptin being used with an appropriate chemotherapy regimen per Table 1?**
                        - Yes
                          - Deny
                        - No
                          - **Is it associated with a high-risk feature? (App B)**
                            - Yes
                              - Deny
                            - No
                              - **Is the breast cancer node-negative?**
                                - Yes
                                  - Adjuvant treatment
                                - No
                                  - No
          - **Is it associated with a high-risk feature? (App B)**
            - Yes
              - Deny
            - No
              - **No**
    - **No**
      - **Is the breast cancer node-negative?**
        - Yes
          - Deny
        - No
          - **Is Herceptin being used with an appropriate chemotherapy regimen per Table 1?**
            - Yes
              - **What is the intent of treatment?**
                - Adjuvant treatment
            - No
              - Deny
      - **No**
Figure 2. Kadcyla Algorithm

1. Is diagnosis HER2-positive MBC? Yes/No
   - No: Deny
   - Yes: Previous received Herceptin and a taxane, separately or in combination for metastatic disease?
     - No: Disease recurrence during or within six months of completing adjuvant therapy?
       - No: Deny
       - Yes: Is Kadcyla being used as a single agent?
         - No: Deny
         - Yes: Currently receiving Kadcyla?
           - No: Document baseline ALT/AST, total bilirubin, LVEF
             - Approve 3 months
           - Yes: Disease progression or unmanageable toxicity since starting Kadcyla? (App D)
             - No: Approve 6 months
             - Yes: Deny
Background
Breast cancer is the most common cancer in women and is second only to lung cancer as a cause of cancer death. The American Cancer Society estimates that 234,580 new cases of breast cancer and 40,030 breast cancer-related deaths will occur in the United States in 2013. Although most patients present with an early stage of breast cancer initially, about 6% to 10% of patients present with metastatic breast cancer. While metastatic breast cancer cannot be cured, therapy focuses on prolonging survival, maintaining quality of life, and delaying disease progression. The median survival for metastatic breast cancer is approximately 18 to 30 months.
Treatment options for metastatic breast cancer include endocrine therapy (e.g., tamoxifen, letrozole), chemotherapy (e.g., anthracyclines, taxanes), and targeted agents, such as HER2 targeted agents (i.e., trastuzumab, lapatinib) and angiogenesis inhibitors (i.e., bevacizumab).6,7 The selection of therapy is based on a number of disease-related and patient-related factors which include tumor biology (hormonal receptors, HER2 status), disease-free interval, previous therapies and response, tumor burden (number and site of metastases), comorbidities, menopausal status, patient age, need for rapid disease/symptom control, and patient preferences. Evaluation of HER2 overexpression is important as it is associated with increased rates of recurrence, tumor aggressiveness, and decreased overall survival.7 Of note, approximately 20% of breast cancers have increased amounts of the HER2 protein.

Herceptin is a recombinant DNA-derived humanized anti-HER2 monoclonal antibody.1 Herceptin is indicated for the treatment of HER2 overexpressing breast cancer and for the treatment of HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. Herceptin also has a compendial use for the treatment of esophageal cancer.10 Kadcyla is a HER2-targeted antibody and microtubule inhibitor conjugate.2 The antibody component is trastuzumab and the microtubule inhibitor is the small molecule cytotoxin, DM1. Binding of DM1 to tubulin disrupts microtubule networks in the cell resulting in cell cycle arrest and apoptotic cell death.2 Similar to Herceptin, Kadcyla has been shown to inhibit HER2 receptor signaling, mediate antibody-dependent cell-mediated cytotoxicity and inhibit shedding of the HER2 extracellular domain in human breast cancer cells that overexpress HER2 in vitro.2 Kadcyla is indicated, as a single agent, for the treatment of patients with HER2-positive metastatic breast cancer who previously received trastuzumab and a taxane separately or in combination.2 Patients should have either received prior therapy for metastatic disease, or developed disease recurrence during or within six months of completing adjuvant therapy.2 Kadcyla cannot be substituted for or with trastuzumab.2

Perjeta is a recombinant humanized monoclonal antibody that is believed to work by targeting a different part of the HER-protein than trastuzumab, resulting in further reduction in growth and survival for HER2-positive breast cancer cells.3,8 The safety and efficacy of Perjeta were evaluated in a randomized, double-blind, placebo-controlled trial enrolling a total of 808 patients with HER2-positive metastatic breast cancer.9 Patients were randomly assigned to receive trastuzumab plus docetaxel and either Perjeta or placebo. The primary endpoint was progression-free survival (PFS). The results showed that patients treated with the combination of Perjeta, trastuzumab, plus docetaxel had a median PFS of 18.5 months. Those treated with trastuzumab, docetaxel, plus placebo combination experienced a PFS of 12.4 months.

Safety
A major component of this policy is to ensure necessary safety concerns are addressed prior to initiating therapy with Herceptin, Kadcyla or Perjeta. Information from the product labeling, U.S. Food and Drug Administration MedWatch, and primary literature are considered. Safety concerns for Herceptin, Kadcyla and Perjeta are summarized in Table 2.

Table 2. Safety Concerns for Herceptin, Kadcyla and Perjeta1-3
**CLINICAL POLICY**

**HER2 Breast Cancer Treatments**

<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Herceptin</th>
<th>Kadcyla</th>
<th>Perjeta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmias, hypertension, cardiac failure, cardiomyopathy, cardiac death</td>
<td>X*</td>
<td></td>
<td>X*</td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td>X*</td>
<td>X*</td>
<td>X*</td>
</tr>
<tr>
<td>Infusion reactions and pulmonary toxicity (e.g., anaphylaxis, angioedema, interstitial pneumonitis, acute respiratory distress syndrome)</td>
<td>X*</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Exposure during pregnancy can result in embryo-fetal death or birth defects</td>
<td>X*</td>
<td>X*</td>
<td>X*</td>
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<tr>
<td>Exacerbation of chemotherapy-induced neutropenia</td>
<td>X</td>
<td></td>
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<tr>
<td>Hepatotoxicity</td>
<td>X*</td>
<td></td>
<td></td>
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<tr>
<td>Hypersensitivity reactions</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Thrombocytopenia</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Neurotoxicity</td>
<td>X</td>
<td></td>
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<tr>
<td>Extravasation</td>
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</table>

X = yes; * Boxed warnings

Herceptin can cause asymptomatic decline in left ventricular ejection fraction (LVEF) and has been associated with left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death. Therefore, LVEF is assessed prior to initiation of Herceptin and at regular intervals during treatment. Herceptin dosing is withheld for at least 4 weeks for either of the following: Greater than or equal to 16% absolute decrease in LVEF from pre-treatment values or LVEF below institutional limits of normal and greater than or equal to 10% absolute decrease in LVEF from pretreatment values. Herceptin may be resumed if, within 4-8 weeks, the LVEF returns to normal limits and the absolute decrease from baseline is \( \leq 15\% \). The use of Herceptin may also induce fetal harm so women of childbearing age and potential should be advised to use contraception. Herceptin use also can result in serious and fatal pulmonary toxicity such as interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Such events can occur as a result of infusion reactions. It is recommended to discontinue Herceptin for severe or life-threatening infusion reactions manifesting as anaphylaxis, angioedema, interstitial pneumonitis or acute respiratory distress syndrome. If severe or life threatening infusion reactions, Herceptin should be discontinued. It may also be necessary to interrupt the infusion in patients with dyspnea or clinically significant hypotension. See Appendix C for toxicities requiring discontinuation of Herceptin.

Kadcyla has been shown to cause hepatotoxicity in the form of asymptomatic transient increases in serum transaminases. Monitoring serum transaminases and bilirubin prior to initiation of Kadcyla treatment and prior to each dose is recommended. Kadcyla also puts patients at increased risk of developing left ventricular dysfunction. A decrease of LVEF to < 40% was seen in patients treated with Kadcyla. Assessing LVEF prior to initiation and at regular intervals (e.g., every three months) during treatment is recommended to ensure LVEF is within normal limits. Management of increased serum transaminases, hyperbilirubinemia, left ventricular dysfunction, thrombocytopenia, pulmonary toxicity or peripheral neuropathy may require temporary interruption. See Appendix D for toxicities requiring discontinuation of Kadcyla.
CLINICAL POLICY  
HER2 Breast Cancer Treatments

Perjeta administration can result in subclinical and clinical cardiac failure. Left ventricular function should be evaluated in all patients prior to and during treatment with Perjeta, and Perjeta should be discontinued for a confirmed clinically significant decrease in left ventricular function. See Appendix E for toxicities requiring discontinuation of Perjeta. The most common adverse reactions in patients treated with Perjeta, trastuzumab, plus docetaxel included diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy. Exposure to Perjeta can result in embryo-fetal death and birth defects. Studies in animals have resulted in oligohydramnios, delayed renal development, and death. Patients should be advised of these risks and the need for effective contraception.

Appendices

Appendix A: Abbreviations
ARDs = acute respiratory distress syndrome  
ALT = alanine aminotransferase  
AST = aspartate aminotransferase  
ER/PR = estrogen receptor/progesterone receptor  
GE = gastroesophageal  
HER = human epidermal growth factor receptor  
LVEF = left ventricular ejection fraction  
MBC = metastatic breast cancer  
MUGA = multi-gated acquisition

Appendix B: Herceptin - HER2-overexpressing breast cancer high-risk features
• ER/PR-negative  
• Tumor size > 2 cm  
• Age < 35 years  
• Histologic and/or nuclear Grade 2 or 3

Appendix C: Herceptin - toxicities that require discontinuation
• Pulmonary toxicity which includes:  
  o Dyspnea  
  o Interstitial pneumonitis  
  o Pulmonary infiltrates  
  o Pleural effusions  
  o Non-cardiogenic pulmonary edema  
  o Pulmonary insufficiency and hypoxia  
  o Acute respiratory distress syndrome  
  o Pulmonary fibrosis  
• Severe or life-threatening infusion reactions  
• Grade 3-4 neutropenia and febrile neutropenia  
• LVEF decrease:  
  o ≥16% absolute decrease in LVEF from pre-treatment values  
  o LVEF below institutional limits of normal and ≥10% absolute decrease in LVEF from pretreatment values  
  o Persistent (>8 weeks) LVEF decline or for suspension of Herceptin dosing on more than 3 occasions for cardiomyopathy

Appendix D: Kadcyla - toxicities that require discontinuation
• Pulmonary toxicity
CLINICAL POLICY
HER2 Breast Cancer Treatments

- Interstitial lung disease
- Pneumonitis
- Infusion-related reactions, hypersensitivity reactions
  - Life threatening infusion-related reaction
- Dose reductions beyond 2.4 mg/kg
- Hepatotoxicity
  - Serum transaminases (AST/ALT)
    - Grade 4 (>20 x ULN)
  - Hyperbilirubinemia
    - Grade 4 (>10 x ULN)
- Concomitant serum transaminases and total bilirubin increases
  - Serum transaminases >3 x ULN
  - Total bilirubin >2 x ULN
- LVEF
  - LVEF < 40% confirmed at 3-week reassessment
  - LVEF 40% to ≤ 45% with decrease ≥ 10% points from baseline and not recovered to within 10% points from baseline at 3-week retest

Appendix E: Perjeta - toxicities that require discontinuation

- Serious hypersensitivity reaction
- LVEF
  - LVEF < 45% with no improvement at a 3-week reassessment
  - LVEF of 45% to 49% with ≥ 10% absolute decrease below the pretreatment value with no improvement at a 3-week reassessment

References
8. FDA News: FDA approves Perjeta for type of late-stage breast cancer. Food and Drug Administration Web site. [http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm307549.htm?utm_c...

<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>Approval Date</th>
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<tbody>
<tr>
<td>Added the treatment regimen for use in metastatic breast cancer in combination with pertuzumab</td>
<td>07/12</td>
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<td>and docetaxel.</td>
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<tr>
<td>Added Kadcyla</td>
<td>06/13</td>
<td>06/13</td>
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<tr>
<td>Renamed to HER2 Breast Cancer Treatments</td>
<td>06/14</td>
<td>06/14</td>
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<tr>
<td>Removed prospective monitoring question from Figure 1</td>
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<tr>
<td>Added Perjeta and Appendices D-G</td>
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<tr>
<td>Updated Appendix C to include docetaxel and pertuzumab as appropriate treatments</td>
<td>08/14</td>
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<tr>
<td>Indications, background, algorithms and appendices edited per package inserts.</td>
<td>04/15</td>
<td>05/15</td>
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<td>Compendial use cited per NCCN guidelines rather than NCCN compendium.</td>
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<tr>
<td>In Figure 1, corrected error of maximum lifetime treatment of 52 weeks, changed to apply to adjuvant treatment only</td>
<td>01/16</td>
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<tr>
<td>Updated disclaimer language and template</td>
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</tbody>
</table>

**Important reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date
of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in 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.

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

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