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

Policy/Criteria
It is the policy of health plans affiliated with Envolve Pharmacy Solutions® that trastuzumab (Herceptin®) is medically necessary when the following criteria are met:

I. Initial Approval Criteria
   A. Nonmetastatic Breast Cancer (must meet all):
      1. Diagnosis of HER-2 positive nonmetastatic breast cancer;
      2. Member meets a or b:
         a. FDA approved use:
            i. One or more of the following disease characteristics:
               1. Node positive disease;
               2. Node negative disease with one or more of the following risk factors:
                  a. ER/PR negative;
                  b. Pathological tumor size >2 cm;
                  c. Histologic and/or nuclear grade 2 or 3;
                  d. Age <35 years;
            ii. Herceptin will be used as adjuvant treatment (treatment given after primary treatment to decrease risk of recurrence) in one of the following ways:
               1. As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel;
               2. With docetaxel and carboplatin;
               3. As a single agent following multi-modality anthracycline-based therapy;
         b. NCCN recommended uses (i, ii or iii):
            i. Herceptin will be used for preoperative systemic therapy in one of the following ways:
               1. In combination with paclitaxel following AC (doxorubicin and cyclophosphamide) regimen as preferred regimen with or without pertuzumab;
               2. In TCH (docetaxel, carboplatin, and trastuzumab) regimen with or without pertuzumab as preferred regimen;
               3. In combination with docetaxel with or without pertuzumab following AC regimen;
               4. In combination with docetaxel and cyclophosphamide;
               5. In combination with pertuzumab and paclitaxel or pertuzumab and docetaxel prior to or following FEC/CEF (fluorouracil, epirubicin, and cyclophosphamide) regimen;
ii. Herceptin will be used as adjuvant systemic therapy in one of the following ways:
   1. In combination with paclitaxel following AC (doxorubicin and cyclophosphamide) regimen as preferred regimen;
   2. In TCH (docetaxel, carboplatin, and trastuzumab) regimen as preferred regimen;
   3. In combination with docetaxel following AC regimen;
   4. In combination with docetaxel and cyclophosphamide;
   5. In TCH regimen (as preferred regimen) with pertuzumab if a pertuzumab-containing regimen was not used as neoadjuvant therapy;
   6. In combination with pertuzumab and paclitaxel (as preferred regimen) or pertuzumab and docetaxel following AC regimen if a pertuzumab-containing regimen was not used as neoadjuvant therapy;
   7. In combination with pertuzumab and paclitaxel or pertuzumab and docetaxel prior to or following FEC/CEF (fluorouracil, epirubicin, and cyclophosphamide) regimen if a pertuzumab-containing regimen was not used as neoadjuvant therapy;

iii. In combination with paclitaxel for low-risk stage I, HER2-positive disease particularly for patients not eligible for other standard adjuvant regimens due to comorbidities.

B. Metastatic and Recurrent Breast Cancer (must meet all):
   1. Diagnosis of recurrent or metastatic HER2-positive breast cancer;
   2. Member meets a or b:
      a. FDA approved use:
         i. Herceptin will be administered in one of the following ways:
            1. In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer;
            2. As a single agent for treatment of HER2-overexpressing breast cancer if member has received one or more chemotherapy regimens for metastatic disease;
      b. NCCN recommended uses (i or ii):
         i. Men or postmenopausal women and must meet all the following:
            1. Disease is estrogen receptor-positive;
            2. Herceptin will be used in combination with aromatase inhibition
            3. If member is a man, he should be receiving concomitant treatment for suppression of testicular steroidogenesis;
         ii. Member meets 1 and 2:
            1. Disease has one or more of the following characteristics:
               a. Hormone receptor-negative;
               b. Hormone receptor-positive and endocrine therapy refractory;
               c. Concomitant symptomatic visceral disease or visceral crisis;
            2. Herceptin will be used in one of the following ways:
a. As preferred first-line therapy in combination with pertuzumab with docetaxel or paclitaxel;  
b. In combination with docetaxel, vinorelbine, or capecitabine or with paclitaxel with or without carboplatin;  
c. As treatment for trastuzumab-exposed HER2-positive disease in combination with carboplatin, cisplatin, cyclophosphamide, eribulin, gemcitabine, ixabepilone, lapatinib (without cytotoxic therapy), or albumin-bound paclitaxel;  
d. In combination with pertuzumab with or without cytotoxic therapy (e.g., vinorelbine or taxane) for one line of therapy beyond first-line therapy in patients previously treated with chemotherapy and trastuzumab in the absence of pertuzumab.

C. Metastatic Gastric and Esophageal Adenocarcinomas (must 1 or 2):  
1. FDA approved use:  
   i. Diagnosis of HER-2 positive metastatic gastric or gastroesophageal junction adenocarcinoma  
   ii. Herceptin will be administered in combination with cisplatin and capecitabine or 5-fluorouracil;  
   iii. Member has not received prior treatment for metastatic disease;  
2. NCCN recommended use:  
   i. Diagnosis of advanced HER2-neu protein overexpressing esophageal, esophagogastric junction, or gastric adenocarcinoma;  
   ii. Herceptin will be used palliative therapy in combination with systemic chemotherapy.

D. Central Nervous System Cancer (must meet all):  
1. NCCN recommended use:  
   a. Herceptin will be used for intracerebrospinal fluid (CSF) treatment for leptomeningeal metastases from breast cancer;  
   b. Herceptin will be used in one of the following ways:  
      1. As induction therapy for primary treatment of good-risk patients with normal CSF flow;  
      2. As maintenance therapy for patients with negative CSF cytology or for clinically stable patients with persistently positive CSF cytology;  
      3. As postinduction therapy for patients with positive CSF cytology.

E. Non-Small Cell Lung Cancer (NSCLC) (must meet all):  
1. NCCN recommended use:  
   a. Herceptin will be used for HER2-positive NSCLC characterized by one of the following histologies:  
      i. Adenocarcinoma (with mixed subtypes);  
      ii. Squamous cell carcinoma;  
      iii. Large cell carcinoma.
F. Other diagnoses/indications: Refer to ERX.SPMN.16 - Global Biopharm Policy.

Approval duration: 3 months

II. Continued Approval
A. Breast, Esophageal/Gastric, CNS, and Lung Cancer (must meet all):
   1. Currently receiving medication via health plan benefit or member has previously met all initial approval criteria.

   Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2):
   1. Currently receiving medication via health plan benefit and documentation supports positive response to therapy; or
   2. Refer to ERX.SPMN.16 - Global Biopharm Policy.

   Approval duration: 3 months

Background
Description/Mechanism of Action:
Herceptin (trastuzumab) is a humanized IgG1 kappa monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. Trastuzumab is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. The HER2 (or c-erbB2) proto-oncogene encodes a transmembrane receptor protein of 185 kDa, which is structurally related to the epidermal growth factor receptor. Herceptin has been shown, in both in vitro assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2. Herceptin is a mediator of antibody-dependent cellular cytotoxicity (ADCC). In vitro, Herceptin-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

Formulations:
Herceptin is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous administration. Each multi-use vial of Herceptin contains 440 mg trastuzumab, 400 mg α,α-trehalose dihydrate, 9.9 mg L-histidine HCl, 6.4 mg L-histidine, and 1.8 mg polysorbate 20, USP. Reconstitution with 20 mL of the appropriate diluent (BWFI or SWFI) yields a solution containing 21 mg/mL trastuzumab at a pH of approximately 6.

FDA Approved Indications:
Herceptin (trastuzumab) is a HER2/new receptor antagonist/formulation for intravenous infusion with the following indications:
- Adjuvant Breast Cancer
Herceptin is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature breast cancer
  
  as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
  
  with docetaxel and carboplatin
  
  as a single agent following multi-modality anthracycline based therapy.

• Metastatic Breast Cancer
  
o Herceptin is indicated:
    
    In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
    
    As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

• Metastatic Gastric Cancer
  
o Herceptin is indicated, 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.

Appendices

Appendix A: Abbreviation Key

CNS: central nervous system

ER/PR: estrogen receptor/progesterone receptor

HER2: human epidermal growth factor receptor 2 protein

NSCLC: non-small cell lung cancer

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

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Reviews, Revisions, and Approvals

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Policy created.
References

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.

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