Medical Policy

Utilization Management and Clinical Medical Policy

Policy Name:	Policy Number:	Scope:	Origination Date:	Effective Date:
Trastuzumab Agents	**MP-RX-FP-161-24**	☒ **MMM MA** ☒ **MMM MultiHealth**	**12/9/2024** **Last Review Date:** **5/6/2026**	**5/6/2026** **Frequently Revision:** **Annual**

Service Category:

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

Service Description:

This document addresses the use of Herceptin Hylecta (trastuzumab; hyaluronidase) and Herceptin (trastuzumab) biosimilar products which include Hercessi, Herzuma, Ogivri, Ontruzant, Kanjinti, and Trazimera, a drug approved by the Food and Drug Administration (FDA) for the treatment of HER2-overexpressing breast cancer and HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

Background Information:

Herceptin (trastuzumab) is a monoclonal antibody that selectively targets the extracellular domain of the Human Epidermal Growth Factor Receptor 2 (HER2), which is overexpressed in certain cancers, including breast and gastric malignancies. Since its FDA approval in 1998, trastuzumab has revolutionized the treatment of HER2-positive cancers, significantly improving survival rates and patient outcomes. HER2 is a transmembrane receptor tyrosine kinase that regulates cell growth, differentiation, and survival. Overexpression or amplification of HER2 occurs in approximately 15–30% of breast cancers and 10–30% of gastric and gastroesophageal cancers. These tumors are typically aggressive, with high recurrence rates and poor survival outcomes, making HER2-targeted therapies like trastuzumab critical for their management.

Trastuzumab works through multiple mechanisms to inhibit tumor growth and progression. It downregulates HER2 receptors, induces cell cycle arrest by increasing the cyclin-dependent kinase inhibitor p27, and promotes antibody-dependent cellular cytotoxicity. Additionally, trastuzumab prevents HER2 receptor cleavage by metalloproteases, disrupting tumor cell survival and proliferation pathways. These mechanisms highlight its importance as a targeted therapy for HER2-positive malignancies.

Herceptin is approved for the treatment of HER2-overexpressing breast cancer in both early-stage and metastatic settings, as well as HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. It is administered intravenously, with dosing tailored to the indication. Typical regimens include an initial loading dose of 4 mg/kg IV over 90 minutes, followed by 2 mg/kg IV weekly, or a loading dose of 8 mg/kg IV over 90 minutes, followed by 6 mg/kg IV every three weeks. In the adjuvant setting for breast cancer, treatment may continue for up to one year, while for metastatic breast or advanced gastric cancer, therapy is administered until disease progression or unacceptable toxicity.

Herceptin Hylecta (trastuzumab and hyaluronidase-oysk) is a subcutaneous trastuzumab product and does not have the same indications, dosage, or administration instructions as intravenous trastuzumab products such as Herceptin and its IV biosimilars. Herceptin Hylecta is indicated only for HER2-overexpressing adjuvant breast cancer and HER2-overexpressing metastatic breast cancer in adults. It is not indicated for HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. The recommended dose of Herceptin Hylecta is a fixed 600 mg/10,000 units administered subcutaneously over approximately 2 to 5 minutes once every 3 weeks; no loading dose and no body-weight-based dose adjustment are required, and it must not be administered intravenously. In addition, NCCN breast cancer guidance states that Herceptin Hylecta may be

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substituted for intravenous trastuzumab and used as a single agent or in combination with other systemic therapies for HER2-positive breast cancer. Do not substitute Herceptin Hylecta for or with ado-trastuzumab emtansine or fam-trastuzumab deruxtecan-nxki.

Despite its efficacy, trastuzumab carries risks that require careful monitoring. Cardiac toxicity, including left ventricular dysfunction and congestive heart failure (CHF), is a significant concern, particularly when used with anthracycline-based chemotherapy. Baseline cardiac function tests, including ejection fraction (EF), are required before starting therapy, with ongoing monitoring every three months. Therapy should be discontinued in patients with significant declines in EF or symptoms of CHF. Pregnancy is another critical consideration, as trastuzumab can cause fetal harm, including oligohydramnios, pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Women of childbearing potential should be advised to use effective contraception during treatment and informed of the potential risks.

Trastuzumab can also cause serious infusion-related reactions and pulmonary toxicity, including rare but fatal cases. Symptoms such as dyspnea, significant hypotension, or severe hypersensitivity reactions require immediate intervention and potential discontinuation of the drug. Patients with pre-existing lung disease or extensive pulmonary tumor involvement are at higher risk for severe toxicity. Herceptin is contraindicated in patients with hypersensitivity to trastuzumab or any of its components. Additionally, its safety and efficacy in pediatric patients have not been established.

Herceptin is supplied as a 150 mg single-dose vial for intravenous use. Each 150 mg vial is reconstituted with 7.4 mL of Sterile Water for Injection to yield a solution containing 21 mg/mL trastuzumab. Its ability to selectively target HER2 and disrupt tumor progression has made trastuzumab a cornerstone in the treatment of HER2-positive cancers. Clinical studies consistently show improved overall response rates, progression-free survival, and overall survival in patients treated with trastuzumab. While its use requires careful consideration of associated risks, trastuzumab continues to provide significant benefits for patients with aggressive HER2-positive malignancies, offering hope and improved outcomes for a challenging subset of cancers.

Breast Cancer

According to the National Comprehensive Cancer Network (NCCN), breast cancers can be categorized as being HER2 positive or HER2 negative. HER2-positive breast cancer is faster growing and considered more aggressive. Studies indicate that the drug trastuzumab (Herceptin) is effective in treatment of HER2-positive early stage breast cancer and HER2-positive metastatic breast cancer. Trastuzumab is not effective in the treatment of HER2-negative breast cancers.

In various clinical trials, trastuzumab has demonstrated substantial effectiveness in improving outcomes for women with HER2-positive metastatic and early-stage breast cancer, either as a standalone therapy or in combination with other chemotherapeutic agents. Trastuzumab has been particularly noted for its ability to improve response rates to chemotherapy by 53% and for significantly reducing the risk of breast cancer recurrence by 52% when paired with standard chemotherapy. Although median duration of response and overall survival were extended in patients treated with trastuzumab and chemotherapy, severe cardiotoxicity and increased likelihood of congestive heart failure has been noted as side effects. Ongoing monitoring and management of side effects are paramount to safeguard patient well-being.

Gastric Cancer

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Advanced gastric cancer, characterized by HER2 overexpression in 6% to 35% of cases, remains an incurable disease necessitating the development of new, less toxic treatments. Although HER2 overexpression, driven by gene amplification similar to breast cancer, has been increasingly identified and linked to poor patient outcomes and aggressive disease, the management of gastric cancer, especially in advanced stages, has seen minimal evolution. The ToGA study, a phase III trial, demonstrated the efficacy and safety of trastuzumab in HER2-positive gastric cancer, showing improved median overall survival (OS) and overall response rate (ORR) when combined with chemotherapy, compared to chemotherapy alone. Consequently, trastuzumab has been recognized as a pivotal targeted drug to enhance OS in advanced HER2-positive gastric cancer. However, resistance to trastuzumab has posed significant challenges, prompting exploration into alternative second-line treatments, such as tyrosine kinase inhibitors, pathway inhibitors, and antibody-chemotherapy conjugates, among others, following the failure of trastuzumab-based first-line therapy.

Additional Compendial uses of Herceptin include:

- HER2-positive breast cancer
  - Neoadjuvant therapy
  - Treatment of recurrent, advanced unresectable, or stage IV (M1) disease
  - Treatment for no response to preoperative systemic therapy
- Intra-cerebrospinal fluid (CSF) treatment for leptomeningeal metastases
- HER2- positive esophageal and esophagogastric junction cancer
- HER2- positive uterine serous carcinoma and carcinosarcoma
- HER2-amplified/positive and RAS and BRAF wild-type colorectal cancer
- HER2- positive salivary gland tumor
- HER2-positive biliary tract cancers

HER2 Testing

HER2 protein overexpression and/or gene amplification should be assessed using FDA-approved tests performed by laboratories with demonstrated proficiency. For breast cancer, HER2 interpretation and reporting should follow the current ASCO/CAP HER2 testing guidance. In general, tumors with IHC 3+ or IHC 2+ with ISH amplification are considered HER2-positive for protein overexpression/gene amplification, while tumors with IHC 0, IHC 1+, or IHC 2+/ISH not amplified are considered HER2-negative for protein overexpression/gene amplification. Detailed interpretation of less common ISH result groups should follow the current ASCO/CAP algorithm and laboratory adjudication procedures rather than legacy borderline cutoffs. For metastatic gastric or gastroesophageal junction adenocarcinoma, HER2 testing should use FDA-approved tests appropriate for gastric cancer specimens.

In women with breast cancer, there are two methods of testing for HER2 tumor status: immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). HER2 test results are interpreted as follows:

- HER2 positive status is IHC 3+ or FISH positive
- HER2 negative status is IHC 0, 1+ or FISH negative
- A borderline IHC result of 2+ should be followed by performing a FISH test.
- A borderline FISH result of an average HER2 gene/chromosome 17 ratio of 1.8 to 2.2 (or an average of greater than 4 to less than 6 HER2 gene copies/cell) should be followed by one of the following:
  - Counting additional cells in the tissue sample

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- Retesting with FISH
- Performing an IHC test

Results from both tests are used in the clinical setting, and the results of the tests influence treatment choices for women with breast cancer. The pathology laboratory where the HER2 testing is done should be accredited to perform such testing. It should have quality control procedures in place to ensure that the test is done correctly, and a quality assurance plan to validate (i.e., determine the accuracy of) the HER2 test results.

Biosimilars

The U.S. Food and Drug Administration (FDA) has granted approval to various biosimilar counterparts to Herceptin (trastuzumab), including Ogivri (trastuzumab-dkst) in December 2017, Herzuma (trastuzumab-pkrb) in December 2018, Ontruzant (trastuzumab-dttb) in January 2019, Trazimera (trastuzumab-qyyp) in March 2019, Kanjinti (trastuzumab-anns) in June 2019, and Hercessi in April 2024.

These biosimilars have received approval for all indications sanctioned for the reference product, Herceptin (trastuzumab), which encompasses:

- Addressing HER2-overexpressing breast cancer, and
- Managing HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

The following table lists the agents included in the class according to their FDA approval dates:

Name	Biosimilar name	Dosage vial	FDA Approval Date	FDA Indications		
				Treatment of HER2-overexpressing metastatic breast cancer	Adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer	HER2+ metastatic gastric or gastroesophageal junction adenocarcinoma
Herceptin (Genentech)	trastuzumab	150 mg/vial (IV only)	9/25/1998	X	X	X
Ogivri (Mylan/GMBH)	trastuzumab-dkst	150 mg/vial 420 mg/vial (IV only)	12/01/2017	X	X	X
Herzuma (Teva/Celltrion)	trastuzumab-pkrb	150 mg/vial 420 mg/vial (IV only)	12/14/2018	X	X	X

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Ontruzant (Samsung Bioepsis/ Merck)	trastuzumab-dttb	150 mg/ vial 420 mg/vial (IV only)	1/18/ 2019	X	X	X
Herceptin Hylecta (Genentech)	trastuzumab; hyaluronidase-oysk	120 mg/2,000 units/mL (SC only)	2/28/2019	X	X	
Trazimera (Pfizer)	trastuzumab-qyyp	150 mg/ vial 420 mg vial (IV only)	3/11/2019	X	X	X
Kanjinti (Amgen)	trastuzumab-anns	150 mg vial 420 mg vial (IV only)	6/13/2019	X	X	X
Hercessi (Accord Biopharma)	trastuzumab-strf	150 mg/vial (IV only)	04/5/2024	X		X

Herceptin Hylecta®, Herceptin®, and its biosimilars carry a boxed warning regarding possible risks for cardiomyopathy, infusion reactions, pulmonary toxicity, and embryo-fetal toxicity. Trastuzumab use can result in cardiac failure that manifests as congestive heart failure (CHF) or decreased left ventricular ejection fraction (LVEF) with greatest risk when administered concurrently with anthracyclines.

Definitions and Measures

- Adjuvant or adjunctive treatment: Treatment given after the primary treatment to increase the chances of a cure and may include chemotherapy, radiation, hormone or biological therapy.
- Biosimilar drug: Biological product that gains approval based on evidence proving it to be highly similar to an already FDA-approved biological product, referred to as a reference product, and that no clinically significant differences exist between the biosimilar and the reference product.
- 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: Treatment given before the main treatment, with the goal of making the main treatment more likely to be successful.
- 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.

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Approved Indications

A. Treatment of HER2-overexpressing metastatic breast cancer. (IV trastuzumab products and Herceptin Hylecta).
B. Adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer. (IV trastuzumab products and Herceptin Hylecta).
C. HER2+ metastatic gastric or gastroesophageal junction adenocarcinoma. (IV trastuzumab products only)

Other Uses

A. See background section above.

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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.

Herceptin Hylecta (trastuzumab; hyaluronidase) and Herceptin (trastuzumab) biosimilar products (Hercessi, Herzuma, Ogivri, Ontruzant, Kanjinti, and Trazimera)

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.)*

Herceptin Hylecta (trastuzumab; hyaluronidase) and Herceptin (trastuzumab) and biosimilar products (Hercessi, Herzuma, Ogivri, Ontruzant, Kanjinti, and Trazimera)

i. Individual has a diagnosis of HER2-positive (HER2+) **Invasive Breast Cancer or Inflammatory Breast Cancer** confirmed by *one* of the following (Label, NCCN 1, 2A):
   A. Immunohistochemistry (IHC) is 3 +; **OR**
   B. In situ hybridization (ISH) positive;
   AND
   C. Individual is using in one of the following ways:
      1. Individual is using trastuzumab as neoadjuvant (preoperative systemic) therapy (NCCN 2A) as part of a regimen/protocol listed in an approved compendium (NCCN), including any of the following:
         a. as a component of TCH (docetaxel, carboplatin, and trastuzumab) regimen (preferred regimen); **OR**
         b. as a component of TCHP (docetaxel, carboplatin, trastuzumab, and pertuzumab) regimen (preferred regimen); **OR**
         c. in combination with docetaxel with or without pertuzumab following AC regimen; **OR**
         d. in combination with paclitaxel, carboplatin and pertuzumab; **OR**
         e. in combination with paclitaxel following AC (doxorubicin and cyclophosphamide) regimen (dose-dense or every 3 weeks); **OR**
         f. in combination with paclitaxel and pertuzumab following AC regimen (dose-dense or every 3 weeks) (both useful in certain circumstances); **OR**
         g. in combination with docetaxel and cyclophosphamide (useful in certain circumstances); **OR**
         h. in combination with paclitaxel and pertuzumab (useful in certain circumstances); **OR**
         i. Individual is using as part of any other regimen/protocol listed by the approved compendia (NCCN).

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OR

2. Individual is using as <u>adjuvant therapy following definitive surgery</u>; **AND**
    a. Individual is using as part of a regimen/protocol listed in an approved compendium (NCCN), including any of the following:
        i. in combination with paclitaxel following AC (doxorubicin and cyclophosphamide) regimen (dose-dense or every 3 weeks); **OR**
        ii. as a component of TCH (docetaxel, carboplatin, and trastuzumab) regimen (preferred regimen); **OR**
        iii. in combination with docetaxel following AC regimen; **OR**
        iv. in combination with docetaxel and cyclophosphamide (useful in certain circumstances); **OR**
        v. Individual is using as part of any other regimen/protocol listed by the approved compendia (NCCN);

    OR

    b. If Individual has disease that is node positive (pN+), they are using in any of the following ways:
        i. in combination with paclitaxel, carboplatin and pertuzumab; **OR**
        ii. as a component of TCHP (docetaxel, carboplatin, trastuzumab and pertuzumab) regimen (preferred regimen); **OR**
        iii. in combination with pertuzumab and paclitaxel following AC regimen (dose-dense or every 3 weeks) (both useful in certain circumstances); **OR**
        iv. in combination with pertuzumab and docetaxel following AC regimen; **OR**
        v. in combination with paclitaxel and pertuzumab (useful in certain circumstances);

    OR

    c. Individual is using trastuzumab in combination with paclitaxel for pT1,N0,M0, HER2-positive breast cancer, particularly if the primary cancer is hormone receptor-negative, in accordance with NCCN Compendium;

    OR

    d. Individual is using as part of any other regimen/protocol listed by the approved compendia (NCCN).

OR

3. Individual is using as <u>maintenance therapy following completion of planned adjuvant chemotherapy</u>; **AND**
    a. Individual is using as part of a regimen/protocol listed in an approved compendium (NCCN), including any of the following:
        i. with or without pertuzumab; **AND**

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1. Individual had node negative disease at initial staging; **AND**
2. If no residual disease after preoperative therapy, or no preoperative therapy was given: complete up to 1 year of HER2-targeted therapy with trastuzumab (with pertuzumab when appropriate); **OR**
3. If residual invasive disease remains after preoperative therapy: ado-trastuzumab emtansine is the preferred adjuvant therapy; if it is discontinued for toxicity, then trastuzumab-based completion is reasonable; **AND**
4. Ado-trastuzumab was tried and had to be discontinued for toxicity, **OR**

ii. with pertuzumab; **AND**

1. Individual had positive nodes at initial staging; **AND**
2. If no residual disease after preoperative therapy, or no preoperative therapy was given: complete up to 1 year of HER2-targeted therapy with trastuzumab (with pertuzumab when appropriate); **OR**
3. If residual invasive disease remains after preoperative therapy: ado-trastuzumab emtansine is the preferred adjuvant therapy; if it is discontinued for toxicity; **OR**

iii. Individual is using as part of any other regimen/protocol listed by the approved compendia (NCCN).

OR

4. Individual has recurrent, unresectable (local or regional) or Stage IV (Metastatic) hormone receptor-positive (HR+), HER2-positive disease; **AND**
   a. Individual is using in combination with tamoxifen, fulvestrant, or an aromatase inhibitor with or without lapatinib; **AND**
      i. Individual has recurrent, unresectable, or metastatic HR-positive/HER2-positive breast cancer and is receiving trastuzumab-based therapy in combination with endocrine therapy in accordance with current NCCN Compendium; **OR**
   b. Individual is using as part of any other regimen/protocol listed by the approved compendia (NCCN

OR

5. Individual has recurrent, unresectable (local or regional) or Stage IV (Metastatic) that is either hormone receptor-negative (HR-) or Hormone receptor positive (HR+), HER2-positive disease (individual may or may not be using hormone therapy); **AND**
   a. Individual is using as part of a regimen/protocol listed in an approved compendium (NCCN), including any of the following:

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i. As first line therapy in combination with pertuzumab with either docetaxel or paclitaxel (NCCN 1); **OR**
   1. Individual is using trastuzumab as part of a regimen listed in the current NCCN Compendium for recurrent, unresectable, or metastatic HER2-positive breast cancer, including trastuzumab + pertuzumab + taxane as a preferred first-line option, and trastuzumab + capecitabine + tucatinib as an NCCN-supported later-line option, particularly for patients with active CNS involvement; **OR**

ii. In combination with pertuzumab with or without cytotoxic therapy (eg, vinorelbine or taxane) (NCCN 2A); **AND**
   1. Individual is using for one line of therapy; **AND**
   2. Individual was previously treated with chemotherapy and trastuzumab in the absence of pertuzumab; **OR**

iii. Individual is using as part of any other regimen/protocol listed by the approved compendia (NCCN).

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ii. Individual has **Esophageal and Esophagogastric Junction Adenocarcinoma (NCCN 1, 2A)**; **AND**
   A. Individual has HER2 positive adenocarcinoma confirmed by one of the following:
      1. Immunohistochemistry (IHC) is **3+**; **OR**
      2. Immunohistochemistry (IHC) is **2+** and **ISH/FISH positive**; **AND**
   B. Individual is using in one of the following ways:
      1. Individual is using as palliative therapy and is not a surgical candidate or has unresectable locally advanced, recurrent, or metastatic disease; **AND**
         a. Individual has Karnofsky performance score ≥60% or ECOG performance score ≤2; **AND**
         b. Individual is using as first-line therapy in combination with any of the following systemic chemotherapy:
            i. in combination with fluorouracil or capecitabine and oxaliplatin or cisplatin (preferred); **OR**
            ii. in combination with fluorouracil and irinotecan; **OR**
            iii. in combination with paclitaxel with or without carboplatin or cisplatin; **OR**
            iv. in combination with docetaxel with or without cisplatin; **OR**
            v. in combination with fluorouracil; **OR**
            vi. in combination with capecitabine; **OR**
            vii. in combination with docetaxel, cisplatin or oxaliplatin, and fluorouracil; **OR**

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viii. Individual is using as part of any other regimen/protocol listed by the approved compendia (NCCN).

OR

2. Individual is using as palliative therapy; **AND**
   a. Individual is not a surgical candidate or has unresectable locally advanced, recurrent, or metastatic disease; **AND**
   b. Individual has HER2 (ERBB2)-positive adenocarcinoma and PD-L1 CPS ≥1; **AND**
   c. Individual has Karnofsky performance score ≥60% or ECOG performance score ≤2; **AND**
   d. Individual is using as preferred first-line therapy in combination with pembrolizumab as part of a regimen/protocol listed in an approved compendium (NCCN), including any of the following:
      i. with fluorouracil, cisplatin or oxaliplatin, and pembrolizumab (preferred); **AND**
         1. Individual has had no prior checkpoint inhibitor therapy; **OR**
         2. Individual had no tumor progression while on therapy with a checkpoint inhibitor; **OR**
      ii. with capecitabine, cisplatin or oxaliplatin, and pembrolizumab (preferred); **AND**
         1. Individual has had no prior checkpoint inhibitor therapy; **OR**
         2. Individual had no tumor progression while on therapy with a checkpoint inhibitor;

OR

iii. Individual is using as part of any other regimen/protocol listed by the approved compendia (NCCN).

OR

iii. Individual has **<u>Gastric Adenocarcinoma (NCCN 1, 2A)</u>**; **AND**
   A. Individual has HER2 (ERBB2)-positive adenocarcinoma confirmed by one of the following:
      1. Immunohistochemistry (IHC) is 3+; OR
      2. Immunohistochemistry (IHC) is 2+ and ISH/FISH positive

   AND
   B. Individual is using in one of the following ways:
      1. Individual is using as primary treatment and is medically fit for surgery but has <u>surgically unresectable locoregional disease</u>; **AND**
         a. Individual is using as part of a regimen/protocol listed in an approved compendium (NCCN), including any of the following:

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i. In combination with fluorouracil or capecitabine and oxaliplatin or cisplatin (preferred) (NCCN 1); **OR**
ii. in combination with fluorouracil and irinotecan; **OR**
iii. in combination with paclitaxel with or without carboplatin or cisplatin; **OR**
iv. in combination with docetaxel with or without cisplatin; **OR**
v. in combination with fluorouracil; **OR**
vi. in combination with capecitabine; **OR**
vii. in combination with docetaxel, cisplatin or oxaliplatin, and fluorouracil; **OR**
viii. Individual is using as part of any other regimen/protocol listed by the approved compendia (NCCN).

OR

2. Individual is using as preferred primary treatment in combination with pembrolizumab-containing regimen (NCCN 1); **AND**
   a. Individual is medically fit for surgery but has surgically unresectable locoregional disease; **AND**
   b. Individual has PD-L1 CPS ≥ 1; **AND**
   c. Individual is using in any of the following regimens:
      i. in combination with cisplatin, pembrolizumab and fluorouracil or capecitabine (preferred); **OR**
      ii. in combination with oxaliplatin, pembrolizumab and fluorouracil or capecitabine (preferred).
      iii. Individual is using as part of any other regimen/protocol listed by the approved compendia (NCCN).

OR

3. Individual is using as palliative therapy and is not a surgical candidate or has unresectable locally advanced, recurrent, or metastatic disease (including peritoneal-only metastatic disease, including positive cytology); **AND**
   a. Individual has Karnofsky performance score ≥60% or ECOG performance score ≤2; **AND**
   b. Individual is using as first-line therapy in combination with any of the following systemic chemotherapy:
      i. in combination with fluorouracil or capecitabine and oxaliplatin or cisplatin (preferred); **OR**
      ii. in combination with fluorouracil and irinotecan; **OR**
      iii. in combination with paclitaxel with or without carboplatin or cisplatin; **OR**
      iv. in combination with docetaxel with or without cisplatin; **OR**
      v. in combination with fluorouracil; **OR**
      vi. in combination with capecitabine; **OR**
      vii. in combination with docetaxel, cisplatin or oxaliplatin, and fluorouracil;

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viii. Individual is using as part of any other regimen/protocol listed by the approved compendia (NCCN).

OR

4. Individual is using as palliative first-line therapy in combination with pembrolizumab; **AND**
   a. Individual is not a surgical candidate or has unresectable locally advanced, recurrent, or metastatic disease (including peritoneal-only metastatic disease, including positive cytology); **AND**
   b. Individual has PD-L1 CPS ≥ 1; **AND**
   c. Individual has Karnofsky performance score ≥ 60% or ECOG performance score ≤ 2; **AND**
   d. Individual has had no prior checkpoint inhibitor therapy or had no tumor progression while on therapy with a checkpoint inhibitor; **AND**
   e. Individual is using in any of the following ways:
      i. with cisplatin, pembrolizumab and fluorouracil or capecitabine; **OR**
      ii. with oxaliplatin, pembrolizumab and fluorouracil or capecitabin; **OR**
      iii. Individual is using as part of any other regimen/protocol listed by the approved compendia (NCCN).

OR

iv. Individual has **colorectal adenocarcinoma,** including colon cancer and rectal adenocarcinoma, that is locally unresectable, medically inoperable, or metastatic **(NCCN 2A)**; **AND**
   A. Individual has HER2-positive/amplified disease; **AND**
   B. The tumor is RAS and BRAF wild-type; **AND**
   C. Trastuzumab will be used in combination with tucatinib or pertuzumab; **AND**
   D. Individual has had no previous treatment with a HER2 inhibitor; **AND**
   E. Individual meets one of the following criteria:
      1. Individual is receiving less intensive therapy; **AND**
         a. Individual meets one of the following biomarker/immunotherapy criteria:
            i. Individual has proficient mismatch repair/microsatellite-stable (pMMR/MSS) disease; **OR**
            ii. Individual has mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) disease or polymerase epsilon/delta (POLE/POLD1) mutation with ultra-hypermutated phenotype and is ineligible for or has progressed on checkpoint inhibitor immunotherapy; **AND**
         b. Individual meets one of the following clinical criteria:
            i. as primary treatment for locally unresectable or medically inoperable disease; **OR**

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ii. as primary treatment for synchronous abdominal/peritoneal metastases that are nonobstructing, or following local therapy for individuals with existing or imminent obstruction; **OR**
iii. as primary treatment for synchronous unresectable metastases at other sites; **OR**
iv. as initial treatment for unresectable metachronous metastases in individuals 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**
v. as subsequent therapy.

OR

2. Individual is receiving initial treatment in combination with pertuzumab or tucatinib for unresectable metachronous metastases; **AND**
   a. Individual has received previous FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CAPEOX (capecitabine and oxaliplatin) within the past 12 months; **AND**
   b. Individual meets one of the following biomarker/immunotherapy criteria:
      i. Individual has proficient mismatch repair/microsatellite-stable (pMMR/MSS) disease; **OR**
      ii. Individual has mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) disease or polymerase epsilon/delta (POLE/POLD1) mutation with ultra-hypermutated phenotype and is not a candidate for immunotherapy.

OR

v. Individual has **Biliary Tract Cancer, including Gall Bladder Adenocarcinoma, Intrahepatic Cholangiocarcinoma, and Extrahepatic Cholangiocarcinoma** that is unresectable or resected gross residual (R2), or metastatic **(NCCN 2A)**;; **AND**
   A. Individual has HER2 positive disease (IHC 3+, ISH positive, or NGS amplification); **AND**
   B. Individual has progression on or after systemic treatment; **AND**
   C. Trastuzumab will be used in combination with tucatinib or pertuzumab; **AND**
   D. The intended use of trastuzumab aligns with NCCN guidelines and is supported by at least a 2A level of evidence.

OR

vi. Individual has **Endometrial Carcinoma, including Uterine Serous Carcinoma and Carcinosarcoma (NCCN 1, 2A)**; **AND**
   A. Individual has Stage III/IV Disease; **AND**
      1. Disease is HER2 Positive; **AND**
      2. Individual has one of the following histologies:

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a. Uterine serous carcinoma; **OR**
b. Carcinosarcoma; **AND**

3. Individual is using trastuzumab in combination with carboplatin and paclitaxel and continued as a single agent for maintenance therapy (preferred); **AND**
4. Individual is using in one of the following ways:
   a. Individual is suitable for primary surgery; **AND**
      i. Individual is using as additional treatment after total hysterectomy/bilateral salpingo-oophorectomy (TH/BSO), with or without sequential external beam radiation therapy (EBRT) and with or without vaginal brachytherapy; **OR**
   b. Individual is not suitable for primary surgery; **AND**
      i. Individual is using as primary treatment, with or without sequential EBRT and with or without brachytherapy.

OR

B. Individual has Recurrent Disease**; AND**
1. Disease is HER2-positive**; AND**
2. Individual has one of the following histologies:
   a. Uterine serous carcinoma**; OR**
   b. Carcinosarcoma**;**
   AND
3. Individual has not received prior trastuzumab therapy**; AND**
4. Individual is using trastuzumab as first-line therapy or as second-line or subsequent therapy when clinically appropriate**; AND**
5. Individual is using trastuzumab in combination with carboplatin and paclitaxel and continued as a single agent for maintenance therapy **(**preferred); **AND**
6. Individual is using in one of the following ways:
   a. for isolated metastases; **OR**
   b. for disseminated metastases, with or without sequential palliative EBRT**; OR**
   c. with sequential EBRT and with or without brachytherapy for locoregional recurrence in individuals with no prior radiation therapy to the site of recurrence or previous vaginal brachytherapy only; **OR**
   d. after surgical exploration, with sequential EBRT and with or without brachytherapy for locoregional recurrence confined to the vagina or paravaginal soft tissue; **OR**
   e. after surgical exploration, with sequential EBRT for locoregional recurrence not confined to the vagina or paravaginal soft tissue in individuals with pelvic or para-aortic lymph node disease; **OR**
   f. after surgical exploration, with or without sequential EBRT for locoregional recurrence not confined to the vagina or paravaginal soft tissue in individuals with microscopic residual upper abdominal/peritoneal disease; **OR**

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g. with or without sequential palliative EBRT or brachytherapy for locoregional recurrence in individuals who have received prior EBRT to the site of recurrence.

OR

vii. Individual has **breast cancer with limited or extensive brain metastasis** that are recurrent or relapsed (NCCN1, 2A); **AND**

A. Disease is HER2 Positive; **AND**

B. Individual will use trastuzumab in *one* of the following ways:

1. In combination with capecitabine and tucatinib (NCCN 1); **AND**
   a. Individual has been previously treated with at least one anti-HER2-based regimen in the metastatic setting; **AND**
   b. Individual meets one of the following criteria:
      i. Has limited brain metastases and meets one of the following:
         1. Use is as initial treatment in select cases (e.g., small asymptomatic brain metastases); **OR**
         2. Has recurrent brain metastases; **OR**
         3. Has relapsed disease with stable systemic disease or reasonable systemic treatment options; **OR**
      ii. Has extensive brain metastases and meets one of the following:
         1. Use is as primary treatment in select cases (e.g., small asymptomatic brain metastases); **OR**
         2. Has recurrent disease with stable systemic disease or reasonable systemic treatment options; **OR**
2. In high dose in combination with pertuzumab (NCCN 2A); **AND**
   a. Has limited brain metastases and meets one of the following:
      i. Use is as initial treatment in select cases (e.g., small asymptomatic brain metastases); **OR**
      ii. Has recurrent brain metastases; **OR**
      iii. Has relapsed disease with stable systemic disease or reasonable systemic treatment options; **OR**
   b. Has extensive brain metastases and meets one of the following:
      i. Use is as primary treatment in select cases (e.g., small asymptomatic brain metastases); **OR**
      ii. Has recurrent disease with stable systemic disease or reasonable systemic treatment options; **OR**

C. The intended use of trastuzumab aligns with NCCN guidelines and is supported by at least a 2A level of evidence;

OR

viii. Individual has **Leptomeningeal Metastases from HER2-positive breast cancer (NCCN 2A)**; **AND**

A. Disease is HER2 Positive; **AND**

B. Trastuzumab will be used as intra-cerebrospinal fluid (CSF) treatment; **AND**

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C. Individual meets one of the following criteria:
   1. Intra-CSF trastuzumab will be used as primary treatment and the individual has good risk status, including all of the following:
      a. Karnofsky Performance Status (KPS) ≥ 60; **AND**
      b. No major neurologic deficits; **AND**
      c. Minimal systemic disease; **AND**
      d. Reasonable systemic treatment options if needed; **OR**
   2. Intra-CSF trastuzumab will be used as maintenance treatment and the individual meets one of the following:
      a. Has negative CSF cytology; **OR**
      b. Is clinically stable with persistently positive CSF cytology; **AND**

D. The intended use of trastuzumab aligns with NCCN guidelines and is supported by at least a 2A level of evidence.

OR

ix. Individual has recurrent unresectable or metastatic **HER2-positive Salivary Gland Adenocarcinoma** (NCCN 2A); **AND**

A. Individual has one of the following:
   1. recurrent disease with distant metastases; **OR**
   2. unresectable locoregional recurrence or second primary with prior radiation therapy; **AND**

B. Individual has a performance status (PS) of 0–3; **AND**

C. Individual will use trastuzumab as systemic therapy in one of the following ways:
   1. as a single agent; **OR**
   2. in combination with docetaxel; **OR**
   3. in combination with pertuzumab; **AND**

D. The intended use of trastuzumab aligns with NCCN guidelines and is supported by at least a 2A level of evidence.

x. Individual has **Small Bowel Adenocarcinoma (NCCN 2A)**; **AND**

A. Individual has advanced or metastatic disease; **AND**

B. Disease is HER2 (ERBB2)-positive/overexpression-amplified; **AND**

C. The tumor is RAS and BRAF wild-type; **AND**

D. Individual is using trastuzumab as second-line or subsequent therapy; **AND**

E. Trastuzumab will be used in one of the following ways:
   1. in combination with pertuzumab, if not previously given; **OR**
   2. in combination with tucatinib, if not previously given.

xi. Individual has **Appendiceal Adenocarcinoma (NCCN 2A)**; **AND**

A. Individual has HER2 (ERBB2)-positive/amplified disease; **AND**

B. The tumor is RAS and BRAF wild-type; **AND**

C. Individual is using trastuzumab as second-line or subsequent therapy; **AND**

D. Trastuzumab will be used in combination with pertuzumab or tucatinib, if not previously given; **AND**

E. Individual has one of the following:

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1. recurrence with serial tumor marker elevation or radiographic progression and progressive or positive findings; **OR**
2. biopsy-proven recurrence of high-risk disease if cytoreductive surgery was previously received or not possible; **OR**
3. progressive disease or inadequate response after neoadjuvant systemic therapy for metastatic peritoneal-only disease; **OR**
4. extraperitoneal disease.

B. Criteria For Continuation of Therapy

i. MMM considers continuation of trastuzumab agents' 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 therapy duration 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 (every six months).

ii. In those cases where trastuzumab is used as adjuvant or neoadjuvant therapy for breast cancer, it will be approved for a total of 12 months of therapy.

C. Authorization Duration

i. Initial Approval Duration: Up to 6 months
ii. Reauthorization Approval Duration: Up to 6 months

D. Conditions Not Covered

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

i. Requests for trastuzumab agents may not be approved when the above criteria (Section A: Criteria for Initial Approval) are not met and for all other indications.

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Limits or Restrictions:

A. Therapeutic Alternatives

This medical policy may be subject to Step Therapy. Please refer to the document published on the MMM Website: https://www.mmm-pr.com/planes-medicos/formulario-medicamentos

B. 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.

Use	Limit
Adjuvant Treatment of HER2-Overexpressing Breast Cancer	- Herceptin®, Herzuma®, Ogivri®, Ontruzant®, Trazimera®, Kanjinti®, Hercessi®: Initial dose of 4 mg/kg over 90 minute IV infusion, then 2 mg/kg over 30 minute IV infusion weekly for 12 weeks (with paclitaxel or docetaxel) or 18 weeks (with docetaxel/carboplatin). One week after the last weekly dose of Herceptin, administer 6 mg/kg as an IV infusion over 30–90 minutes every three weeks to complete a total of 52 weeks of therapy, or - Initial dose of 8 mg/kg over 90 minutes IV infusion, then 6 mg/kg over 30–90 minutes IV infusion every three weeks for 52 weeks. - Herceptin Hylecta®: 600 mg/10,000 units (600 mg trastuzumab and 10,000 units hyaluronidase) administered subcutaneously over approximately 2-5 minutes once every three weeks.
Metastatic HER2-Overexpressing Breast Cancer	- Herceptin®, Herzuma®, Ogivri®, Ontruzant®, Trazimera®, Kanjinti®, Hercessi®: Initial dose of 4 mg/kg as a 90 minute IV infusion followed by subsequent weekly doses of 2 mg/kg as 30 minute IV infusions. - Herceptin Hylecta: 600 mg/10,000 units (600 mg trastuzumab and 10,000 units hyaluronidase) administered subcutaneously over approximately 2-5 minutes once every three weeks.
Metastatic HER2-Overexpressing Gastric Cancer	- Herceptin®, Herzuma®, Ogivri®, Ontruzant®, Trazimera®, Kanjinti®, Hercessi®: Initial dose of 8 mg/kg over 90 minutes IV infusion, followed by 6 mg/kg over 30 to 90 minutes IV infusion every 3 weeks.
Exceptions	
Trastuzumab IV is administered as a loading dose followed by a maintenance dose. Please see the FDA drug label for the FDA approved indications and dosages.	

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Codes Information:

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.

ICD-10 Diagnostic Codes:

ICD-10	Description
C15.3	Malignant neoplasm of upper third of esophagus
C15.4	Malignant neoplasm of middle third of esophagus
C15.5	Malignant neoplasm of lower third of esophagus
C15.8	Malignant neoplasm of overlapping sites of esophagus
C15.9	Malignant neoplasm of esophagus, unspecified
C16.0	Malignant neoplasm of cardia
C16.1	Malignant neoplasm of fundus of stomach
C16.2	Malignant neoplasm of body of stomach
C16.3	Malignant neoplasm of pyloric antrum
C16.4	Malignant neoplasm of pylorus
C16.5	Malignant neoplasm of lesser curvature of stomach, unspecified
C16.6	Malignant neoplasm of greater curvature of stomach, unspecified
C16.8	Malignant neoplasm of overlapping sites of stomach
C16.9	Malignant neoplasm of stomach, unspecified
C17.0 – C17.9	Malignant neoplasm of small intestine
C18.1	Malignant neoplasm of appendix
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

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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
C77.0	Secondary and unspecified malignant neoplasm of lymph nodes of head, face and neck
C77.1	Secondary and unspecified malignant neoplasm of intrathoracic lymph nodes
C77.2	Secondary and unspecified malignant neoplasm of intra-abdominal lymph nodes
C77.3	Secondary and unspecified malignant neoplasm of axilla and upper limb lymph nodes
C77.4	Secondary and unspecified malignant neoplasm of inguinal and lower limb lymph nodes
C77.5	Secondary and unspecified malignant neoplasm of intrapelvic lymph nodes
C77.8	Secondary and unspecified malignant neoplasm of lymph nodes of multiple regions
C77.9	Secondary and unspecified malignant neoplasm of lymph node, unspecified
C78.00	Secondary malignant neoplasm of unspecified lung
C78.01	Secondary malignant neoplasm of right lung
C78.02	Secondary malignant neoplasm of left lung

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C78.1	Secondary malignant neoplasm of mediastinum
C78.2	Secondary malignant neoplasm of pleura
C78.30	Secondary malignant neoplasm of unspecified respiratory organ
C78.39	Secondary malignant neoplasm of other respiratory organs
C78.4	Secondary malignant neoplasm of small intestine
C78.5	Secondary malignant neoplasm of large intestine and rectum
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C78.80	Secondary malignant neoplasm of unspecified digestive organ
C78.89	Secondary malignant neoplasm of other digestive organs
C79.00	Secondary malignant neoplasm of unspecified kidney and renal pelvis
C79.01	Secondary malignant neoplasm of right kidney and renal pelvis
C79.02	Secondary malignant neoplasm of left kidney and renal pelvis
C79.10	Secondary malignant neoplasm of unspecified urinary organs
C79.11	Secondary malignant neoplasm of bladder
C79.19	Secondary malignant neoplasm of other urinary organs
C79.2	Secondary malignant neoplasm of skin
C79.32	Secondary malignant neoplasm of cerebral meninges
C79.40	Secondary malignant neoplasm of unspecified part of nervous system
C79.49	Secondary malignant neoplasm of other parts of nervous system
C79.51	Secondary malignant neoplasm of bone
C79.52	Secondary malignant neoplasm of bone marrow
C79.60	Secondary malignant neoplasm of unspecified ovary
C79.61	Secondary malignant neoplasm of right ovary
C79.62	Secondary malignant neoplasm of left ovary
C79.63	Secondary malignant neoplasm of bilateral ovaries
C79.70	Secondary malignant neoplasm of unspecified adrenal gland
C79.71	Secondary malignant neoplasm of right adrenal gland
C79.72	Secondary malignant neoplasm of left adrenal gland
C79.82	Secondary malignant neoplasm of genital organs
C79.89	Secondary malignant neoplasm of other specified sites
D37.3	Neoplasm of uncertain behavior of appendix.

HCPCS Codes:

Codes	Description
J9356	Injection, trastuzumab, 10 mg and hyaluronidase-oysk (Herceptin Hylecta)
J9355	Injection, trastuzumab, excludes biosimilar, 10 mg
Q5112	Injection, trastuzumab-dttb, biosimilar, (Ontruzant), 10 mg
Q5113	Injection, trastuzumab-pkrb, biosimilar, (Herzuma), 10 mg
Q5114	Injection, Trastuzumab-dkst, biosimilar, (Ogivri), 10 mg
Q5116	Injection, trastuzumab-qyyp, biosimilar, (Trazimera), 10 mg
Q5117	Injection, trastuzumab-anns, biosimilar, (Kanjinti), 10 mg
Q5146	Injection, trastuzumab-strf (Hercessi), biosimilar, 10 mg

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    b. Esophageal and Esophagogastric Junction Cancers. Version 2.2026.
    c. Gastric Cancer. Version 2.2026.
    d. Biliary Tract Cancers. Version 1.2026.
    e. Colon Cancer. Version 1.2026.
    f. Uterine Neoplasms. Version 2.2026.
    g. Central Nervous System Cancers. Version 3. 2025.
    h. Head and Neck Cancers. Version 1.2026.
    i. Small Bowel Adenocarcinoma. Version 1.2026.

Policy Name:	Policy Number:	Scope:	Origination Date:	Effective Date:
Trastuzumab Agents	MP-RX-FP-161-24	☒ MMM MA ☒ MMM MultiHealth	12/9/2024	5/6/2026
			Last Review Date: 5/6/2026	Frequently Revision: Annual

j. Appendiceal Neoplasms and Cancers. Version 1.2026.

14. Herceptin® (trastuzumab) for injection, for intravenous use: Prescribing information. (2024, June). U.S. Food and Drug Administration. Retrieved March 31, 2026.
15. Herceptin Hylecta® (trastuzumab and hyaluronidase-oysk) injection, for subcutaneous use: Prescribing information.(2024, June). U.S. Food and Drug Administration. Retrieved March 31, 2026.
16. Hercessi™ (trastuzumab-strf) for injection, for intravenous use: Prescribing information. (2024, April). U.S. Food and Drug Administration. Retrieved March 31, 2026.
17. Herzuma® (trastuzumab-pkrb) for injection, for intravenous use: Prescribing information. (2024, November). U.S. Food and Drug Administration. Retrieved March 31, 2026.
18. Ogivri® (trastuzumab-dkst) for injection, for intravenous use: Prescribing information. (2024, November). U.S. Food and Drug Administration. Retrieved March 31, 2026.
19. Ontruzant® (trastuzumab-dttb) for injection, for intravenous use: Prescribing information. (2025, March). U.S. Food and Drug Administration. Retrieved March 31, 2026.
20. Kanjinti® (trastuzumab-anns) for injection, for intravenous use: Prescribing information. (2024, December). U.S. Food and Drug Administration. Retrieved March 31, 2026.
21. Trazimera™ (trastuzumab-qyyp) for injection, for intravenous use: Prescribing information. (2025, August). U.S. Food and Drug Administration. Retrieved March 31, 2026.

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.

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Policy History:

Type of Review	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Annual Review	Updated policy description: Added Hyclecta NCCN substitution/use recommendation and the non-substitution warning, updated Herceptin dosage form, and updated the HER2 Testing subsection. Specified FDA approved uses by product. Updated Criteria for Initial Approval to align with current NCCN guidelines, including new criteria for Small Bowel Adenocarcinoma and Appendiceal Neoplasms and Cancers. Coding Reviewed: Added ICD-10 codes C17.0-C17.9, C18.1, and D37.3; HCPCS Code Q5146. Completed an administrative adaptation to the new policy format/template for consistency across sections. Updated references.	5/1/2026	5/6/2026
Annual Review	Minimal changes: word formatting. No coding changes	7/17/2025	8/8/2025
Policy Inception	New Medical Policy Creation	12/9/2024	12/9/2024