Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Trastuzumab Agents	MP-RX-FP-161-24	☒ MMM MA ☒ MMM Multihealth

Service Category

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

Service Description

This document addresses the use Hylecta (trastuzumab; hyaluronidase) and Herceptin (trastuzumab), biosimilar products which include Ogivri, Herzuma, Ontruzant, Trazimera, Kanjinti, and Hercessi, 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.
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 440 mg vial of intravenous powder, reconstituted with 20 mL of Bacteriostatic Water for Injection, USP (1.1% benzyl alcohol), resulting in a 21 mg/mL solution. 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

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 HER2 gene amplification assessments should be conducted using FDA-approved tests, specialized for breast or gastric cancers, in proficient laboratories. Particularly for metastatic gastric cancer, utilizing FDA-approved tests tailored for gastric cancers is crucial due to unique histopathological differences from breast cancers, such as incomplete membrane staining and more frequently observed heterogeneous HER2 expression. Incorrect assay performance, like using inadequately fixed tissue, not using specified reagents, deviating from specific assay instructions, or failing to incorporate suitable controls for assay validation, may yield unreliable results.

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
    - Retesting with FISH

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- 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

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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
Herzuma (Teva/Celltrion)	trastuzumab-pkrb	150 mg/vial 420 mg/vial (IV only)	12/14/2018	X	X	X
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
Hercessi (Shanghai Henlius Biotech, Inc.)	**trastuzumab-strf**	150 mg/vial (IV only)	04/25/2024	X	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

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- 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.

FDA-Approved 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

Other Uses

N/A

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Applicable Codes

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

HCPCS	Description
J9356	Injection, trastuzumab, 10 mg and hyaluronidase-oysk (Herceptin Hylecta)
J9355	Injection, trastuzumab, excludes biosimilar, 10 mg
Q5113	Injection, trastuzumab-pkrb, biosimilar, (Herzuma), 10 mg
Q5117	Injection, trastuzumab-anns, biosimilar, (Kanjinti), 10 mg
Q5114	Injection, Trastuzumab-dkst, biosimilar, (Ogivri), 10 mg
Q5112	Injection, trastuzumab-dttb, biosimilar, (Ontruzant), 10 mg
Q5116	Injection, trastuzumab-qyyp, biosimilar, (Trazimera), 10 mg
J3590	Unclassified biologics (when specified as Hercessi), 10 mg

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
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

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ICD-10	Description
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
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

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ICD-10	Description
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
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

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ICD-10	Description
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

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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.

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

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

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

I. Individual has a diagnosis of HER2-positive (HER2+) **Invasive Breast Cancer or Inflammatory Breast Cancer** confirmed by *one* of the following:
   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).

OR

2. Individual is using as <u>adjuvant therapy (immediately following mastectomy)</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**
        vi. Individual is using in combination with paclitaxel; **AND**
            1. Individual has low-risk T1, N0, M0 breast cancer; **AND**
            2. Individual is not eligible for other standard adjuvant regimens due to comorbidities (preferred regimen); **OR**
        vii. 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**

1. Individual had node negative disease at initial staging; **AND**
2. There was no residual disease after preoperative therapy (neoadjuvant) or the individual didn't receive preoperative therapy; **OR**
3. Residual tumor remains after preoperative therapy (including node-positive after preoperative therapy); **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 the patient has residual disease after preoperative therapy, Ado-trastuzumab was used and had to be discontinued due to toxicity; **OR**
3. There was no residual disease after preoperative therapy (neoadjuvant); **OR**

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

OR

4. Individual has <u>recurrent, unresectable (local or regional) or Stage IV (Metastatic) hormone receptor-positive (HR+),</u> HER2-positive disease; **AND**
   a. Individual is using in combination with tamoxifen, fulvestrant, or an aromatase inhibitor with or without lapatinib; **AND**
   b. Individual meets one of the following criteria:
      i. Is a postmenopausal woman; **OR**
      ii. Is a premenopausal woman undergoing ovarian ablation or suppression**; OR**
      iii. Is a a premenopausal woman without ovarian ablation or suppression, using trastuzumab in combination in tamoxifen (not with fulvestrant, or an aromatase inhibitor); **OR**
   c. Individual is using as part of any other regimen/protocol listed by the approved compendia (NCCN

OR

5. Individual has <u>recurrent, unresectable (local or regional) or Stage IV (Metastatic) that is either hormone receptor-negative (HR-) or Hormone receptor positive (HR+),</u> 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:

i. As first line therapy in combination with pertuzumab with either docetaxel or paclitaxel (NCCN 1); **OR**
ii. As third-line therapy and beyond, or in the second line setting, in combination with capecitabine and tucatinib; **AND**
    1. Individual has both systemic and CNS progression in the third line setting and beyond (NCCN 1); **OR**
iii. As fourth-line therapy and beyond in combination with (NCCN 2A):
    1. With docetaxel, vinorelbine, or capecitabine, or with paclitaxel with or without carboplatin; **OR**
    2. With cyclophosphamide, eribulin, gemcitabine, ixabepilone, lapatinib (without cytotoxic therapy), or albumin-bound paclitaxel; **OR**
iv. 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**
v. Individual is using as part of any other regimen/protocol listed by the approved compendia (NCCN).

OR

II. Individual has **Esophageal and Esophagogastric Junction Adenocarcinoma**; **AND**
    A. Individual has HER2 positive adenocarcinoma;
    AND
        1. Individual is using as palliative treatment to relieve dysphagia and has a planned esophagectomy; **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 fluorouracil or capecitabine and oxaliplatin or cisplatin and pembrolizumab in patients with PD-L1 CPS ≥1 (NCCN 1); **OR**
                ii. in combination with fluorouracil or capecitabine and oxaliplatin or cisplatin (preferred) (NCCN 1); **OR**
                iii. in combination with fluorouracil and irinotecan; **OR**
                iv. in combination with paclitaxel with or without carboplatin or cisplatin; **OR**
                v. in combination with docetaxel with or without cisplatin; **OR**
                vi. in combination with fluorouracil; **OR**
                vii. in combination with capecitabine; **OR**

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viii. in combination with docetaxel, cisplatin or oxaliplatin, and fluorouracil; **OR**

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

OR

2. Individual has unresectable locally advanced, recurrent, or metastatic disease or is not candidate for surgery; **AND**
    a. Individual has Karnofsky performance score ≥60% or ECOG performance score ≤2; **AND**
    b. Individual is using as part of a regimen/protocol listed in an approved compendium (NCCN), including any of the following:
        i. Individual is using as first-line therapy in combination with any of the following systemic chemotherapy that does not include pembrolizumab:
            1. fluorouracil or capecitabine and oxaliplatin or cisplatin (preferred) (NCCN 1); **OR**
            2. fluorouracil and irinotecan; **OR**
            3. paclitaxel with or without carboplatin or cisplatin; **OR**
            4. docetaxel with or without cisplatin; **OR**
            5. fluorouracil; **OR**
            6. capecitabine; **OR**
            7. docetaxel, cisplatin or oxaliplatin, and fluorouracil; **OR**

        OR

        ii. Individual is using in combination with pembrolizumab (NCCN 1); **AND**
            1. Individual has PD-L1 CPS ≥ 1; **AND**
            2. Trastuzumab is used as first line therapy; **AND**
            3. Documentation is provided confirming that the individual had no prior tumor progression while on therapy with a checkpoint inhibitor; **AND**
            4. Individual is usng in any of the following ways:
                a. with fluorouracil, cisplatin or oxaliplatin, and pembrolizumab; **OR**
                b. with capecitabine, cisplatin or oxaliplatin, and pembrolizumab.

        OR

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

OR

III. Individual has **Gastric Adenocarcinoma**; **AND**

A. Individual has HER2 overexpression positive adenocarcinoma;
AND

B. Individual has early-stage cancer after endoscopic resection (NCCN 2A); **AND**

OR

C. Individual has surgically unresectable disease but is medically fit for surgery; **AND**

AND

D. Individual is using as part of a regimen/protocol listed in an approved compendium (NCCN), including any of the following:

a. In combination with any of the following chemotherapies not including pembrolizumab:

i. fluorouracil or capecitabine and oxaliplatin or cisplatin (preferred) (NCCN 1); **OR**

ii. fluorouracil and irinotecan; **OR**

iii. paclitaxel with or without carboplatin or cisplatin; **OR**

iv. docetaxel with or without cisplatin; **OR**

v. fluorouracil; **OR**

vi. capecitabine; **OR**

vii. docetaxel, cisplatin or oxaliplatin, and fluorouracil; **OR**

b. In a pembrolizumab-containing regimen (NCCN 1); **AND**

i. Individual has PD-L1 CPS ≥ 1; **AND**

ii. Individual is using in any of the following regimens:

1. in combination with cisplatin, pembrolizumab and fluorouracil or capecitabine (preferred); **OR**
2. in combination with oxaliplatin, pembrolizumab and fluorouracil or capecitabine (preferred).

OR

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

OR

E. Individual is not candidate for surgery or has unresectable locally advanced, recurrent, or metastatic disease; **AND**

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1. Individual has Karnofsky performance score ≥60% or ECOG performance score ≤2; **AND**
2. Individual is using as part of a regimen/protocol listed in an approved compendium (NCCN), including any of the following:
    a. Individual is using as first-line therapy in combination with any of the following systemic chemotherapy that does not include pembrolizumab:
        i. fluorouracil or capecitabine and oxaliplatin or cisplatin (preferred); **OR**
        ii. fluorouracil and irinotecan; **OR**
        iii. paclitaxel with or without carboplatin or cisplatin; **OR**
        iv. docetaxel with or without cisplatin; **OR**
        v. fluorouracil; **OR**
        vi. capecitabine; **OR**
        vii. docetaxel, cisplatin or oxaliplatin, and fluorouracil;

    OR

    b. Individual is using in combination with pembrolizumab; **AND**
        i. Individual has PD-L1 CPS ≥ 1; **AND**
        ii. Trastuzumab is used as first line therapy; **AND**
        iii. Documentation is provided confirming that the individual had no prior tumor progression while on therapy with a checkpoint inhibitor; **AND**
        iv. Individual is usng in any of the following ways:
            1. with cisplatin, pembrolizumab and fluorouracil or capecitabine; **OR**
            2. with oxaliplatin, pembrolizumab and fluorouracil or capecitabin; **OR**
    c. Individual is using as part of any other regimen/protocol listed by the approved compendia (NCCN).

OR

IV. Individual **has colon cancer (adenocarcinoma) that is unresectable, inoperable, advanced, or metastatic, including colorectal cancer, rectal adenocarcinoma, appendiceal adenocarcinoma, and anal adenocarcinoma**, and will use trastuzumab according to an indication listed in the approved compendium (NCCN) with at least a 2A level of evidence, including:
    A. Individual has HER2-positive/amplified disease; **AND**
    B. The tumor is negative (wild-type) for RAS and BRAF mutations; **AND**
    C. Trastuzumab will be used in combination with tucatinib, pertuzumab, or lapatinib; **AND**
    D. Individual meets one of the following criteria (as recommended by NCCN):

1. Is not appropriate for intensive therapy; **OR**
2. Has received prior therapy for the disease (as defined by NCCN for the patient's condition/stage); **AND**

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

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; **AND**

A. Individual has HER2 positive disease; **AND**
B. Individual will use after systemic treatment; **AND**
C. Trastuzumab will be used in combination with tucatinib, pertuzumab, or lapatinib; **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**; **AND**

A. Individual has Stage III/IV Disease; **AND**
1. Disease is HER2 Positive; **AND**
2. Is using (or used) as Neoadjuvant (prior to surgery) in combination with carboplatin and paclitaxel; **AND**
3. Is continuing use as maintenance after primary surgery; **OR**
4. Individual is using as maintenance therapy for disease that is not suitable for surgery as primary treatment; **AND**
5. The intended use of trastuzumab aligns with NCCN guidelines and is supported by at least a 2A level of evidence;

OR

B. Individual has Recurrent Disease; **AND**
1. Disease is HER2 Positive; **AND**
2. Individual has not received prior trastuzumab therapy; **AND**
3. Individual is using (or used) in combination with carboplatin and paclitaxel; **AND**
4. Is continuing use as maintenance after primary surgery; **AND**
5. Individual is not using trastuzumab for isolated metastasis; **AND**
6. The intended use of trastuzumab aligns with NCCN guidelines and is supported by at least a 2A level of evidence;

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OR

VII. Individual has **Limited or Extensive Brain Metastasis** that are recurrent or relapsed (NCCN1); AND
   A. Disease is HER2 Positive; **AND**
   B. Individual has been previously treated with at least one anti-HER2-based regmens; **OR**
   C. If used as primary treatment, the patient has small asymptomatic brain metastasis; **AND**
   D. Individual will use in any of the following ways:
      1. In combination with capecitabine and tucatinib (NCCN 1); **OR**
      2. In high dose in combination with pertuzumab (NCCN 2A); **AND**
   E. 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; **AND**
   A. Disease is HER2 Positive; **AND**
   B. Trastuzumab will be used as intra-cerebrospinal fluid (CSF) treatment; **AND**
   C. 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 **Salivary Gland Adenocarcinoma** (NCCN 2A); **AND**
   A. Individual will use trastuzumab according to an indication listed in the approved compendium (NCCN) with at least a 2A level of evidence, including:
      1. As a single agent; **OR**
      2. In combination with docetaxel; **OR**
      3. In combination with pertuzumab; **AND**
   B. The intended use of trastuzumab aligns with NCCN guidelines and is supported by at least a 2A level of evidence.

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).

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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. N/A

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®, 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

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Use	Limit
	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. 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®, 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. 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®, 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.	

Reference Information

1. Centers for Medicare and Medicaid Services (CMS) Local Coverage Determinations document # L34026. Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=34026&ver=16&keyword=trastuzumab&keywordType=starts&areaId

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8. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Updated periodically.
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10. Kurzrock R, Bowles DW, Kang H, et al. Targeted therapy for advanced salivary gland carcinoma based on molecular profiling: results from MyPathway, a phase IIa multiple basket study. Ann Oncol 2020;31:412-421. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32067683.
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12.
13. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2023 Updated periodically.
14. NCCN Drugs & Biologics Compendium (NCCN Compendium®) 2023 National Comprehensive Cancer Network, Inc. Available at: www.NCCN.org. Updated periodically.

Policy History

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Policy Inception	New Medical Police Creation	12/9/2024	12/17/2024

Revised: 07/01/2024