Medical Policy:

Trastuzumab Injection (Herceptin®, Herceptin Hylecta®, Herzuma®, Kanjinti®, Ontruzant®, Ogivri®, Trazimera®)

POLICY NUMBER	LAST REVIEW	ORIGIN DATE
MG.MM.PH.85	October 27, 2023	January 1, 2021

Length of Authorization

Coverage will be provided for six months and may be renewed.

Dosing Limits [Medical Benefit]

A. Max Units (per dose and over time):

Breast Cancer and Gastric/Esophageal/Gastro-esophageal junction Cancers

	150 mg SDV Load MU	150 mg SDV Maintenance MU
7-day dosing schedule	45	30
21-day dosing schedule	90	75

CNS Cancer

- 150 mg SDV: 15 billable units every 7 days

Uterine Cancer

	150 mg SDV Load MU	150 mg SDV Maintenance MU
21-day dosing schedule	90	75

Dosing and Administration
Herceptin Package Insert

HerceptinHylecta

Herzuma

Kanjinti

Ogivri

Ontruzant

Trazimera

Guideline

For Commercial, Medicaid and Medicare members:

- Non-preferred agents: Herceptin, Herceptin Hylecta, Herzuma, Ontruzant, Ogivri
- Preferred agents: Kanjinti and Trazimera

I. Initial Approval Criteria

Coverage is provided in the following conditions *(in addition to use supported by the National Comprehensive Cancer Network [NCCN] Clinical Practice Guidelines [NCCN Guidelines®] and/or NCCN Drugs & Biologics Compendium [NCCN Compendium®] with a recommendation of category level 1 or 2A*):*

1. Baseline left ventricular ejection fraction (LVEF) within normal limits prior to initiating therapy and will be assessed at regular intervals (e.g., every 3 months) during treatment; **AND**
2. Patient is 18 years or older; **AND**
3. Patient's cancer is human epidermal growth factor receptor 2 (HER2)-positive*****; **AND**
4. For newly started therapy with a non-preferred agent (Herceptin, Herceptin Hylecta, Herzuma, Ontruzant, or Ogivri), for Commercial, Medicaid, and Medicare members:

   Coverage may be considered medically necessary when:

   a. Patient has experienced a therapeutic failure or intolerance with the plan-preferred medications (Kanjinti AND Trazimera); **OR**
   b. The non-preferred agent is requested for an indication for which the plan-preferred biosimilar agents (Kanjinti or Trazimera) have not been FDA-approved OR are not supported by NCCN Guidelines® or NCCN Compendium® with a recommendation of category level 1 or 2A; **AND**

**Please note: Coverage for an appropriate biosimilar substitution will be allowed where NCCN Guidelines or Compendium state that an FDA-approved biosimilar is an appropriate substitution for trastuzumab.*

Breast cancer †

1. Used as adjuvant therapy; **AND**

   A. Patient has locally advanced, node positive, or inflammatory disease; **AND**

      i. Used in combination with a taxane-based regimen (e.g., docetaxel, paclitaxel, etc.) with or without pertuzumab; **OR**

      ii. Used as a single agent; **OR**

      iii. Used in combination with pertuzumab; **OR**

2. Used as neoadjuvant or preoperative therapy; **AND**

   A. Patient has locally advanced, node positive, or inflammatory disease; **AND**

   B. Used in combination with a taxane-based regimen (e.g., docetaxel, paclitaxel, etc.) with or without pertuzumab; **OR**

3. Used for recurrent unresectable or metastatic disease **OR** inflammatory breast cancer; **AND**

   A. Used as a single agent in patients who have received one or more prior chemotherapy regimens for metastatic disease †; **OR**

   B. Used in combination with one of the following:

      i. Paclitaxel as first-line therapy for metastatic disease †

      ii. Endocrine therapy (e.g., tamoxifen, fulvestrant, or aromatase inhibition with or without lapatinib) in patients with hormone-receptor positive disease; **AND**

         a. Patient is post-menopausal; **OR**

         b. Patient is pre-menopausal and is treated with ovarian ablation/suppression; **OR**

         c. Patient is a male (sex assigned at birth)

      iii. Pertuzumab and a taxane (e.g., docetaxel, paclitaxel) as first-line therapy

      iv. Capecitabine and tucatinib as second-line therapy and beyond

      v. Cytotoxic chemotherapy as third-line therapy and beyond

      vi. Lapatinib (without cytotoxic therapy) as third-line therapy and beyond

      vii. Pertuzumab with or without cytotoxic therapy as subsequent therapy in patients previously treated with chemotherapy and trastuzumab (without pertuzumab)

Central Nervous System Cancer ‡

1. Patient has leptomeningeal metastases from breast cancer; **AND**
2. Herceptin will be administered intrathecally; **OR**
3. Patient has brain metastases from breast cancer; **AND**

   A. Used in combination with ONE of the following:

      i. Pertuzumab

      ii. Capecitabine and tucatinib in patients previously treated with at least one HER2-directed regimen; **AND**

   B. Used in ONE of the following treatment settings:

i. Used as initial treatment in patients with small asymptomatic brain metastases

ii. Patient has recurrent limited brain metastases

iii. Patient has recurrent extensive brain metastases with stable systemic disease or reasonable systemic treatment options

iv. Patient has relapsed limited brain metastases with either stable systemic disease or reasonable systemic treatment options

Gastric, Esophageal and Esophagogastric Junction Cancers †

1. Patient is not a surgical candidate or has unresectable locally advanced, recurrent, or metastatic adenocarcinoma; **AND**
2. Used as first-line therapy in combination with chemotherapy with or without pembrolizumab (excluding use in combination with DCF [docetaxel, carboplatin, and fluorouracil])

Uterine Cancer ‡

1. Used in combination with carboplatin and paclitaxel; **AND**
2. Used for advanced or recurrent uterine serous carcinoma

† FDA Approved Indication(s); **‡** Compendia recommended Indication(s)

*****HER2-positive overexpression criteria:
1. Immunohistochemistry (IHC) assay 3+; **OR** 2. Fluorescence in situ hybridization (FISH) assay ≥2.0 (HER2/CEP17 ratio); **OR** 3. Average HER2 copy number ≥ 6 signals/cell

iii. Renewal Criteria

Coverage can be renewed based upon the following criteria:

1. Continuation of documented current and/or successful therapy with a non-preferred agent (Herceptin, Herceptin Hylecta, Herzuma, Ontruzant or Ogivri); **AND**
2. Tumor response with stabilization of disease or decrease in size of tumor or tumor spread; **AND**
3. Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: cardiotoxicity (i.e. left ventricular dysfunction, cardiomyopathy); pulmonary toxicity (i.e. pneumonitis); neutropenia; infusion-related reactions; etc.; **AND**
4. Left ventricular ejection fraction (LVEF) has not had an absolute decrease of more than 15% from baseline and is within normal limits

Breast Cancer (neoadjuvant and adjuvant therapy)

1. Patient has not exceeded a maximum of fifty-two (52) weeks of treatment (total 18 cycles)

Limitations/Exclusions

Herceptin is considered investigational when used for any indication not listed above.

Herceptin Hylecta is indicated for adjuvant breast cancer and metastatic breast cancer.

Herceptin Hylecta is indicated for the adjuvant treatment of HER2-overexpressing node positive or node negative (ER/PR negative or with one high risk feature breast cancer.

1. as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
2. as part of a treatment regimen with docetaxel and carboplatin
3. as a single agent following multi-modality anthracycline based therapy

Herceptin Hylecta is indicated for metastatic breast cancer.

1. In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
2. As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

Herzuma, Kanjinti, Ogivri, **Ontruzant, and Trazimera** are indicated for the treatment of adjuvant breast cancer, metastatic breast cancer, metastatic gastric cancer.

Adjuvant Breast Cancer (Herzuma, Kanjinti, Ogivri, Ontruzant, and Trazimera)
Indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature [see Clinical Studies (14.1)]) breast cancer

1. as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
2. as part of a treatment regimen with docetaxel and carboplatin
3. as a single agent following multi-modality anthracycline based therapy.

Metastatic Breast Cancer (Herzuma, Kanjinti, Ogivri, Ontruzant, and Trazimera)

1. In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
2. As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

Metastatic Gastric Cancer (Herzuma, Kanjinti, Ogivri, Ontruzant, and Trazimera)

1. In combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease.

Applicable Procedure Codes

Code	Description
J9355	Injection, trastuzumab, 10 mg; 1 billable unit = 10mg
C9399	Unclassified drugs or biologicals. Herceptin Hylecta 600-10000 MG-UNT/5ML SOLN
Q5113	Injection, trastuzumab-pkrb, biosimilar, (Herzuma), 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, effective 10/01/2019
Q5117	Injection, trastuzumab-anns, biosimilar, (kanjinti), 10 mg, effective 10/01/2019

Applicable NDCs

Code	Description
50242-0132-xx	Herceptin 150 mg SDV; powder for injection
50242-0077-01	HERCEPTIN HYLECTA 600 mg/10,000 units providing 600 mg trastuzumab and 10,000 units hyaluronidase per 5 mL.
63459-0305-47	HERZUMA (trastuzumab-pkrb) for Injection 420 mg/vial, multi-dose vial
67457-0847-44	Ogivri (trastuzumab-dkst) for injection 420 mg/vial, multi-dose vial
00006-5033-02	Ontruzant (trastuzumab-dttb) for injection 150 mg/vial, single-dose vial
55513-0132-01	vial, 1 each Trastuzumab (Kanjinti) 420mg, Lyophilisate for solution for injection
00069-0305-01	TRAZIMERA (trastuzumab-qyyp) injection 420 mg/vial, multiple-dose vial

ICD-10 Diagnoses

Code	Description
C15.3	Malignant neoplasm of upper third of esophagus
C15.4	Malignant neoplasm of middle third of esophagus
C15.5	Malignant neoplasm of the 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 female breast
C50.022	Malignant neoplasm of nipple and areola, left female breast
C50.029	Malignant neoplasm of nipple and areola, unspecified female 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
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
C54.0	Malignant neoplasm of isthmus uteri
C54.1	Malignant neoplasm of endometrium
C54.2	Malignant neoplasm of myometrium
C54.3	Malignant neoplasm of fundus uteri
C54.8	Malignant neoplasm of overlapping sites of corpus uteri

C54.9	Malignant neoplasm of corpus uteri, unspecified
C55	Malignant neoplasm of uterus, part unspecified
C79.32	Secondary malignant neoplasm of cerebral meninges
D37.1	Neoplasm of uncertain behavior of stomach
D37.8	Neoplasm of uncertain behavior of other specified digestive organs
D37.9	Neoplasm of uncertain behavior of digestive organ, unspecified
Z80.49	Family history of malignant neoplasm of other genital organs
Z85.00	Personal history of malignant neoplasm of unspecified digestive organ
Z85.028	Personal history of other malignant neoplasm of stomach
Z85.3	Personal history of malignant neoplasm of breast

Revision History

Company(ies)	DATE	REVISION
EmblemHealth & ConnectiCare	10/27/2023	Update: Effective 1/1/2024 Removed Ogivri as preferred agent, added to non-preferred agents.
EmblemHealth & ConnectiCare	9/25/2023	Annual Review: Initial Criteria: Added: prior to initiating therapy and will be assessed at regular intervals (e.g., every 3months during treatment, AND" to the following istatement: Baseline left ventricular ejection fraction (LVEF) within normal limits "prior to initiating therapy and will be assessed at regular intervals (e.g., every 3months during treatment, AND" Breast cancer Initial Criteria: Removed: "Used as adjuvant treatment; OR 1. Used as preoperative treatment for breast preservation; OR 2. Used for recurrent or metastatic disease" Added: 1. "Used as adjuvant therapy; AND A. Patient has locally advanced, node positive, or inflammatory disease; AND i. Used in combination with a taxane-based regimen (e.g., docetaxel, paclitaxel, etc.) with or without pertuzumab; OR ii. Used as a single agent; OR viii. Used in combination with pertuzumab; OR 2. Used as neoadjuvant or preoperative therapy; AND A. Patient has locally advanced, node positive, or inflammatory disease; AND B. Used in combination with a taxane-based regimen (e.g., docetaxel, paclitaxel, etc.) with or without pertuzumab; OR

		3. Used for recurrent unresectable or metastatic disease OR inflammatory breast cancer; AND A. Used as a single agent in patients who have received one or more prior chemotherapy regimens for metastatic disease †; OR B. Used in combination with one of the following: i. Paclitaxel as first-line therapy for metastatic disease † ii. Endocrine therapy (e.g., tamoxifen, fulvestrant, or aromatase inhibition with or without lapatinib) in patients with hormone-receptor positive disease; AND a. Patient is post-menopausal; OR b. Patient is pre-menopausal and is treated with ovarian ablation/suppression; OR c. Patient is a male (sex assigned at birth) iii. Pertuzumab and a taxane (e.g., docetaxel, paclitaxel) as first-line therapy ix. Capecitabine and tucatinib as second-line therapy and beyond x. Cytotoxic chemotherapy as third-line therapy and beyond xi. Lapatinib (without cytotoxic therapy) as third-line therapy and beyond xii. Pertuzumab with or without cytotoxic therapy as subsequent therapy in patients previously treated with chemotherapy and trastuzumab (without pertuzumab)" <u>Central Nervous System Cancer Initial Criteria:</u> Added 4. "Patient has brain metastases from breast cancer; AND C. Used in combination with ONE of the following: iii. Pertuzumab iv. Capecitabine and tucatinib in patients previously treated with at least one HER2-directed regimen; AND D. Used in ONE of the following treatment settings: v. Used as initial treatment in patients with small asymptomatic brain metastases vi. Patient has recurrent limited brain metastases vii. Patient has recurrent extensive brain metastases with stable systemic disease or reasonable systemic treatment options viii. Patient has relapsed limited brain metastases with either stable systemic disease or reasonable systemic treatment options"

		Gastric, Esophageal and Esophagogastric Junction Cancers Initial Criteria: Removed: 1. "Used in combination with cisplatin and 5-FU or capecitabine for first-line therapy; AND 5. Patient has metastatic disease" Added: 4. "Patient is not a surgical candidate or has unresectable locally advanced, recurrent, or metastatic adenocarcinoma; AND 5. Used as first-line therapy in combination with chemotherapy with or without pembrolizumab (excluding use in combination with DCF [docetaxel, carboplatin, and fluorouracil])" Renewal Criteria: Added: Breast Cancer (neoadjuvant and adjuvant therapy) Patient has not exceeded a maximum of fifty-two (52) weeks of treatment (total 18 cycles)
EmblemHealth & ConnectiCare	1/17/2023	Transfer to New Template
EmblemHealth & ConnectiCare	12/19/2020	Clarifications: • Step therapy will apply to NEW starts only • NCCN-supported use (with 1 or 2A recommendation) will be covered Renewal criteria updated: • Removed: "Patient continues to meet criteria identified above" Added coverage: "Continuation of documented current and/or successful therapy with a non-preferred agent (Herceptin, Herceptin Hylecta, Herzuma, or Ontruzant)."
EmblemHealth & ConnectiCare	11/2/2020	Effective **01/01/2021**, Member must fail trial of Kanjinti, Ogivri, and Trazimera, prior to using Herceptin, Herceptin Hylecta, Herzuma, or Ontruzant. (Medicare members are subject to this step therapy).
EmblemHealth & ConnectiCare	03/31/2020	Added to the Initial Criteria: Effective 07/01/2020, Kanjinti, Ogivri, and Trazimera are the preferred agents for Commercial and Medicaid members. Member must fail trial of Kanjinti AND Ogivri AND Trazimera prior to using Herceptin, Herceptin Hylecta, Herzuma, and Ontruzant (Only Commercial and Medicaid members are subject to this step therapy).
EmblemHealth & ConnectiCare	03/31/2020	Updated covered indications for Herceptin Hylecta, Herzuma, Kanjinti, Ogivri, Ontruzant, and Trazimera per FDA label
EmblemHealth & ConnectiCare	09/23/2019	Updated Policy to include Kanjinti and Trazimera. Added New codes for Kanjinti Q5117 and Trazimera Q5116.

EmblemHealth & ConnectiCare	9/13/2019	Updated Indication for Herzuma to include metastatic gastric or gastroesophageal junction adenocarcinoma.
EmblemHealth & ConnectiCare	7/1/2019	Added Herceptin Hylecta, Herzuma, Ogivri, and Ontruzant
EmblemHealth & ConnectiCare	1/1/2021	New Policy

References

1. Herceptin [package insert]. South San Francisco, CA; Genentech, Inc; April 2017. Accessed August 2018.
2. Product Information: HERCEPTIN HYLECTA™ subcutaneous injection, trastuzumab hyaluronidase-oysk subcutaneous injection. Genentech Inc (per FDA), South San Francisco, CA, 2019.
3. Product Information: OGIVRI intravenous injection, trastuzumab-dkst intravenous injection. Mylan Pharmaceuticals, Inc (per FDA), Morgantown, WV, 2017.
4. Product Information: ONTRUZANT intravenous injection, trastuzumab-dttb intravenous injection. Merck Sharp & Dohme Corp (per FDA), Whitehouse Station, NJ, 2019.
5. Product Information: HERZUMA® intravenous injection, trastuzumab-pkrb intravenous injection. Teva Pharmaceuticals, Inc (per FDA), North Wales, PA, 2018.
6. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) trastuzumab. National Comprehensive Cancer Network, 2018. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc." To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed August 2018.
7. Zagouri F, Sergentanis TN, Bartsch R, et al. Intrathecal administration of trastuzumab for the treatment of meningeal carcinomatosis in HER2-positive metastatic breast cancer: a systematic review and pooled analysis. Breast Cancer Res Treat 2013; 139:13
8. Fader AN, Roque DM, Siegel E, et al. Randomized Phase II Trial of Carboplatin-Paclitaxel Versus Carboplatin-Paclitaxel-Trastuzumab in Uterine Serous Carcinomas That Overexpress Human Epidermal Growth Factor Receptor 2/neu. J Clin Oncol. 2018 Jul 10;36(20):2044-2051. doi: 10.1200/JCO.2017.76.5966. Epub 2018 Mar 27.
9. First Coast Service Options, Inc. Local Coverage Determination (LCD): Trastuzumab (Herceptin®) (L34026). Centers for Medicare & Medicaid Services, Inc. Updated on 7/7/2017 with effective date 7/14/2017. Accessed August 2018.
10. Palmetto GBA. Local Coverage Article: HERCEPTIN (trastuzumab): Coverage and Billing (A53777). Centers for Medicare & Medicaid Services, Inc. Updated on 1/31/2018 with effective date 2/26/2018. Accessed August 2018.
11. Product Information: KANJINTI™ intravenous injection, trastuzumab-anns intravenous injection. Amgen Inc (per FDA), Thousand Oaks, CA, 2019.

12. Product Information: TRAZIMERA™ intravenous injection, trastuzumab-qyyp intravenous injection. Pfizer Labs (per FDA), New York, NY, 2019.