POLICY: Biosimilars – Herceptin, Herzuma, Ogivri & Ontruzant

- Herceptin® (trastuzumab injection for intravenous infusion – Genentech Inc.)
- Herzuma® (trastuzumab-pkrb injection for intravenous use – Celltrion)
- Ogivri™ (trastuzumab-dkst injection for intravenous use – Mylan)
- Ontruzant® (trastuzumab-dttb injection for intravenous use – Merck)

EFFECTIVE DATE: 1/1/2021
LAST REVISION DATE: 06/28/2023

COVERAGE CRITERIA FOR: All Aspirus Medicare Plans

OVERVIEW

Trastuzumab products are human epidermal growth factor receptor 2 (HER2)/neu receptor antagonists indicated for the following uses:[1]

- **Breast cancer, adjuvant treatment** of HER2-overexpressing node positive or node negative (estrogen receptor[ER]/progesterone receptor [PR] negative or with one high risk feature) 1) as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel; 2) as part of treatment regimen with docetaxel and carboplatin; or 3) as a single agent following multi-modality anthracycline based therapy.
- **Breast cancer, metastatic,** HER2-overexpressing, either in combination with paclitaxel for first-line treatment, or as a single agent in patients who have received one or more chemotherapy regimens for metastatic disease.
- **Gastric cancer or gastroesophageal (GE) junction adenocarcinoma, metastatic**, HER2-overexpressing, in combination with cisplatin and capecitabine or 5-fluorouracil (5-FU) who have not received prior treatment for metastatic disease.

Herzuma, Kanjinti, Ogivri, Ontruzant, and Trazimera are all approved biosimilars for Herceptin; all of the biosimilars have the same FDA-approved indications as Herceptin. For all indications, patients must be selected for therapy based on an FDA-approved companion diagnostic for trastuzumab. Tests are specific for breast cancer or gastric cancer.

Dosing Information

The approved dosing of trastuzumab as *adjuvant treatment of breast cancer* is given for a total of 52 weeks.[1] Initial dose is 4 mg/kg intravenously, then 2 mg/kg weekly for 12 weeks (with paclitaxel or docetaxel) or 18 weeks (with docetaxel/carboplatin). One week after the last weekly dose, trastuzumab 6 mg/kg is given every three weeks to complete a total of 52 weeks of therapy. Another dosing schedule is an initial dose of 8 mg/kg, then 6 mg/kg every 3 weeks for a total of 52 weeks of therapy. Extending adjuvant treatment beyond 1 year is not recommended. The approved dosing for *metastatic breast cancer* is trastuzumab (alone or in combination with paclitaxel) at an initial dose of 4 mg/kg given intravenously followed by weekly doses of 2 mg/kg until disease progression.[1] Many dosing schedules for trastuzumab are included in guidelines.[2] Alternate dosing will be assessed individually on a case-by-case basis.

The approved dose of trastuzumab given with chemotherapy in metastatic gastric cancer is an initial dose of 8 mg/kg intravenously followed by subsequent doses of 6 mg/kg every 3 weeks until progression.[1] Guidelines recommend either trastuzumab 8 mg/kg on Day 1 of Cycle 1 and then 6 mg/kg every 21 days or trastuzumab 6 mg/kg on Day 1 of Cycle 1 and then 4 mg/kg every 14 days for first-line or second-line

therapy (in combination with chemotherapy) for metastatic or locally advanced gastric, esophageal, or GE junction cancer.[3-4]

For colon cancer or rectal cancer, when used in combination with Perjeta® (pertuzumab intravenous infusion), trastuzumab is given as an 8 mg/kg infusion on Day 1 of Cycle 1 followed by 6 mg/kg every 21 days. When used in combination with lapatinib, trastuzumab is given as a 4 mg/kg infusion on Day 1 of Cycle 1, followed by 2 mg/kg weekly.[5-6]

For biliary tract cancer, endometrial carcinoma and salivary gland tumors, in the clinical studies, trastuzumab 8 mg per kg intravenous infusion followed by 6 mg per kg intravenous infusion not more frequently than once every 3 weeks was given.[7,8, 9]

Guidelines

Trastuzumab is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):

- **Breast Cancer:** NCCN guidelines (version 4.2022 – June 21, 2022) recommend trastuzumab in combination with chemotherapy or endocrine therapy for adjuvant treatment of HER2-positive breast cancer (category 1).[2,10] Trastuzumab in combination with paclitaxel (category 2A) is a preferred preoperative/adjuvant therapy regimen. The guidelines also list other trastuzumab-containing regimens for preoperative and adjuvant therapy. The preferred first-line agents for HER2-positive recurrent or metastatic disease (either hormone receptor-negative or hormone receptor-positive and refractory to endocrine therapy) include: Perjeta plus trastuzumab plus docetaxel (category 1) or paclitaxel (category 2A). The guidelines list other trastuzumab-containing regimens for HER2-positive metastatic disease.
- **Colon and Rectal Cancer:** NCCN guidelines for colon cancer (version 1.2022 – February 25, 2022) and NCCN guidelines for rectal cancer (version 1.2022 – February 25, 2022) list trastuzumab in combination with Perjeta or lapatinib tablets in patients with HER2-amplified disease, RAS and BRAF wild-type disease.[3-4,10]
- **Gastric Cancer and Esophageal and Esophagogastric Junction Cancers**: NCCN guidelines (version 2.2022 – February 11, 2022) state that for metastatic, locally advanced or recurrent disease (where local therapy is not indicated) trastuzumab should be added to first-line systemic chemotherapy for HER2-overexpressing adenocarcinoma.[5-6,10] The recommended regimens for metastatic or locally advanced HER2-positive gastric, esophageal, or esophagogastric junction adenocarcinoma are trastuzumab in combination with cisplatin and a fluoropyrimidine (5-FU or capecitabine) [category 1] or trastuzumab in combination with other chemotherapy agents (category 2A/2B) [various regimens based on individual patient characteristics]. Trastuzumab is not recommended for use in combination with anthracyclines.
- **Head and Neck Cancers:** NCCN guidelines (version 2.2022 – April 26, 2022) recommend trastuzumab as a systemic therapy option for recurrent, unresectable, or metastatic salivary gland tumors, (useful in certain circumstances), for HER2-positive tumors as a single agent or in combination with Perjeta or docetaxel (category 2A).[7,10]
- **Hepatobiliary Cancer:** NCCN guidelines (version 1.2022 – March 29, 2022) recommend trastuzumab + Perjeta as subsequent-line therapy for biliary tract cancers for progression on or after systemic treatment for unresectable or metastatic disease that is HER2-positive (category 2A).[8,10]
- **Uterine Neoplasms**: NCCN guidelines (version 1.2022 – November 4, 2021) list the combination chemotherapy regimen of carboplatin/paclitaxel/trastuzumab as one of the recommended therapies for patients with HER2-positive endometrial carcinoma for stage III/IV or recurrent uterine serous carcinoma (category 2A).[9,10]

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Herceptin, Herzuma, Ogivri, and Ontruzant. Approval is recommended for those who meet the Criteria and Dosing for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by an Express Scripts clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with trastuzumab products, as well as the monitoring required for adverse events and long-term efficacy, approval requires Herceptin, Herzuma, Ogivri, and Ontruzant to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Herceptin, Herzuma, Ogivri, and Ontruzant is recommended for request meeting both the biosimilar step therapy requirements and indication requirements.

Biosimilar Step Therapy Requirements (New Starts Only)

Criteria. *The patient must meet the following criteria (A or B):*

A) For patients new to Herceptin, Herzuma, Ogivri, or Ontruzant therapy only, must have a trial of Trazimera, or Kanjinti prior to approval of Herceptin, Herzuma, Ogivri, and Ontruzant. New starts to therapy defined as no use of Herceptin, Herzuma, Ogivri, or Ontruzant within the past 180 days for Medicaid and Commercial patients. New starts to therapy defined as no use of Herceptin, Herzuma, Ogivri, or Ontruzant within the past 365 days for Medicare patients.

B) Patient has a contraindication or other clinical reason why a biosimilar cannot be tried before Herceptin, Herzuma, Ogivri, and Ontruzant.

Note: Biosimilar step only required for indications FDA-Approved for both Herceptin and the biosimilar(s).

FDA-Approved Indications

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1. Breast Cancer. Approve for the duration noted if the patient meets the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND

C) Patient meets ONE of the following criteria (i or ii):

i. Approve for 1 year (total) if trastuzumab is used for neoadjuvant (preoperative)/adjuvant therapy; OR

ii. Approve for 1 year if trastuzumab is used for recurrent or metastatic disease; AND

D) The medication is prescribed by or in consultation with an oncologist.

Dosing: Approve one of the following dosing regimens (A, B, or C):

A) 4 mg/kg intravenously followed by 2 mg/kg not more frequently than once weekly; OR

B) 8 mg/kg intravenously followed by 6 mg/kg not more frequently than once every 3 weeks; OR

C) 4 mg/kg intravenously followed by 2 mg/kg not more frequently than once weekly during chemotherapy, then 6 mg/kg not more frequently than once every 3 weeks.

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2. Gastric, Esophageal, or Gastroesophageal Junction Cancer. Approve for 1 year if the patient meets the following (A, B, C, D, and E):

A) Patient is ≥ 18 years of age; AND

B) Patient has locally advanced or metastatic disease; AND
C) Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
D) Patient meets the following criteria (i and ii):
  i. Trastuzumab will be used as first-line therapy; AND
  ii. Trastuzumab will be used in combination with chemotherapy; AND
  Note: Examples of chemotherapy are cisplatin, oxaliplatin, capecitabine, 5-fluorouracil (5-FU).
E) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve one of the following dosing regimens (A or B):
A) 8 mg/kg intravenously followed by 6 mg/kg not more frequently than once every 3 weeks; OR
B) 6 mg/kg intravenously followed by 4 mg/kg not more frequently than once every 2 weeks.

Other Uses with Supportive Evidence

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3. Biliary Tract Cancer. Approve for 1 year if the patient meets the following (A, B, C, D, E, and F):
A) Patient is ≥ 18 years of age; AND
B) Patient has unresectable or metastatic disease; AND
C) Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
D) The medication will be used in combination with Perjeta (pertuzumab intravenous infusion); AND
E) The patient has tried one systemic regimen; AND
Note: Examples of a systemic regimen include: gemcitabine and cisplatin, 5-fluorouracil and oxaliplatin, capecitabine and oxaliplatin, or gemcitabine and oxaliplatin.
F) The medication is prescribed by or in consultation with an oncologist.

Dosing: Approve 8 mg/kg intravenously followed by 6 mg/kg not more frequently than once every 3 weeks.

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4. Colon or Rectal Cancer. Approve for 1 year if the patient meets the following (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) Patient has advanced or metastatic disease; AND
C) Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
D) The medication is used in combination with Perjeta (pertuzumab intravenous infusion), lapatinib, or Tukysa (tucatinib tablets); AND
E) The medication is prescribed by or in consultation with an oncologist.

Dosing: Approve one of the following dosing regimens (A or B):
A) 8 mg/kg intravenously followed by 6 mg/kg not more frequently than once every 3 weeks; OR
B) 4 mg/kg intravenously followed by 2 mg/kg not more frequently than weekly.

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5. Endometrial Carcinoma. Approve for 1 year if the patient meets the following (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) Patient has advanced or recurrent uterine serous carcinoma; AND
C) Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
D) Trastuzumab will be used in combination with chemotherapy; AND
Note: Examples of chemotherapy are carboplatin, paclitaxel.
E) The medication is prescribed by or in consultation with an oncologist.

Dosing: Approve 8 mg/kg intravenously followed by 6 mg/kg not more frequently than once every 3 weeks.

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6. Salivary Gland Tumor. Approve for 1 year if the patient meets the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has recurrent, unresectable, or metastatic disease; AND
- **C)** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
- **D)** The medication is prescribed by or in consultation with an oncologist.

Dosing: Approve 8 mg/kg intravenously followed by 6 mg/kg not more frequently than once every 3 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of trastuzumab is not recommended in the following situations.

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Herceptin® intravenous infusion [prescribing information]. South San Francisco, CA: Genentech; February 2021.
2. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – March 23, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 21, 2023.
3. The NCCN Colon Clinical Practice Guidelines in Oncology (version 2.2023 – April 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 21, 2023.
4. The NCCN Rectal Clinical Practice Guidelines in Oncology (version 3.2023 – May 26, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 21, 2023.
5. The NCCN Gastric Clinical Practice Guidelines in Oncology (version 1.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 21, 2023.
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7. The NCCN Head and Neck Cancers Clinical Practice Guidelines in Oncology (version 2.2023 – May 15, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 21, 2023.
8. The NCCN Biliary Tract Cancers Clinical Practice Guidelines in Oncology (version 2.2023– May 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 21, 2023.
9. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (version 2.2023 – April 28, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 21, 2023.
10. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 21, 2023. Search term: trastuzumab.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Breast Cancer:** A requirement was added that the patient is ≥ 18 years of age. **Gastric, Esophageal, or Gastroesophageal Junction Cancer:** A requirement was added that the patient is ≥ 18 years of age. **Colon or Rectal Cancer:** A requirement was added that the patient is ≥ 18 years of age. A requirement that the patient has advanced or metastatic disease was added. In the dosing section, the words "up to" was removed from the dosing option. The dose option of 4 mg per kg intravenous infusion followed by 2 mg per kg intravenous infusion not more frequently than weekly was added to the criteria. **Endometrial Carcinoma:** A requirement was added that the patient is ≥ 18 years of age. **Salivary Gland Tumor:** Indication and criteria were added to other uses with supportive evidence based on NCCN guideline recommendations. A requirement was added that the patient is ≥ 18 years of age. Dosing was added as 8 mg per kg intravenous infusion followed by 6 mg per kg intravenous infusion not more frequently than once every 3 weeks.	06/16/2021
Annual Revision	**Biliary Tract Cancer:** Condition of approval, criteria, and dosing were added to other uses with supportive evidence based on NCCN guideline recommendations.	06/29/2022
Annual Revision	**Colon or Rectal Cancer:** Added "Tukysa (tucatinib tablets)" as one of the agents that can be used in combination with trastuzumab.	06/28/2023