

- POLICY:** Oncology (Injectable) – Trastuzumab Products
- Herceptin[®] (trastuzumab injection for intravenous infusion – Genentech Inc.)
 - Herzuma[®] (trastuzumab-pkrb injection for intravenous infusion – Celltrion)
 - Ogivri[™] (trastuzumab-dkst injection for intravenous infusion – Mylan)
 - Ontruzant[®] (trastuzumab-dttb injection for intravenous infusion – Merck)
 - Trazimera[™] (trastuzumab-qyyp injection for intravenous infusion – Pfizer)
 - Kanjinti[™] (trastuzumab-anns injection for intravenous infusion – Amgen)

DATE REVIEWED: 06/10/2020

OVERVIEW

Trastuzumab products are indicated for adjuvant treatment of human epidermal growth factor receptor 2 (HER2) overexpressing node positive or node negative (estrogen receptor [ER]/progesterone receptor [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) with docetaxel and carboplatin; or 3) as a single agent following multi-modality anthracycline-based therapy.¹ They are also indicated for the treatment of HER2-overexpressing metastatic breast cancer, either in combination with paclitaxel for first-line treatment or as a single agent in patients who have received one or more chemotherapy regimens. In addition, Herceptin is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil (5-FU), for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal (GE) junction adenocarcinoma, who have not received prior treatment for metastatic disease. Herzuma, Ogivri, Ontruzant, Trazimera, and Kanjinti 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.

Trastuzumab products are available as lyophilized powder in a single-dose vial containing 150 mg per vial and in multi-use vials containing 420 mg per vial (latter will be discontinued).¹ Trastuzumab should be reconstituted to a 21 mg/mL solution, which should be diluted. Dilute reconstituted trastuzumab solution using 250 mL of 0.9% Sodium Chloride Injection (do not use Dextrose 5% solution). The diluted solution is infused intravenously over 30 to 90 minutes. Trastuzumab should not be administered as an intravenous push or bolus.

Dosing

The approved dosing of Herceptin as *adjuvant treatment of breast cancer* is given for a total of 52 weeks according to one of the following doses and schedules.¹ When given during and following paclitaxel, docetaxel, or docetaxel/carboplatin, the initial Herceptin dose is 4 mg/kg as an intravenous infusion over 90 minutes and then 2 mg/kg over 30 minutes weekly during chemotherapy for the first 12 weeks (paclitaxel or docetaxel) or 18 weeks (docetaxel/carboplatin). One week following the last weekly dose of Herceptin, Herceptin 6 mg/kg is given as an intravenous infusion over 30 to 90 minutes every 3 weeks. A second adjuvant treatment regimen is Herceptin as a single agent within 3 weeks following completing multi-modality, anthracycline-based chemotherapy regimens: the initial dose of Herceptin is 8 mg/kg as an intravenous infusion over 90 minutes and subsequent doses are 6 mg/kg intravenous infusion over 30 to 90 minutes every 3 weeks. Extending adjuvant treatment beyond 1 year is not recommended. The approved dosing for *metastatic breast cancer* is Herceptin (alone or in combination with paclitaxel) at an initial dose of 4 mg/kg given over 90 minutes followed by weekly doses of 2 mg/kg over 30 minutes until disease progression. Many dosing schedules for Herceptin are included in the NCCN guidelines.² Preoperative

therapy is 9 weeks of treatment before surgery with assessment of tumor response during delivery of therapy. Patients with operable breast cancer experiencing progression of disease during preoperative systemic therapy should be taken promptly to surgery. Alternate dosing will be assessed individually on a case-by-case basis.

The approved dose of Herceptin given with chemotherapy in metastatic gastric cancer is an initial dose of 8 mg/kg as a 90-minute infusion that is followed by subsequent doses of 6 mg/kg given over 30 to 90 minutes every 3 weeks until progression.¹ The NCCN guidelines recommend either Herceptin 8 mg/kg on day 1 of Cycle 1 and then 6 mg/kg every 21 days or Herceptin 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.⁵⁻⁶

For endometrial carcinoma, in the clinical study, for the first dose, trastuzumab 8 mg/kg infusion was given with carboplatin/paclitaxel combination chemotherapy over 90-minutes every 21 days.¹⁰ For subsequent cycles, the trastuzumab dose was 6 mg/kg infusion (with carboplatin/paclitaxel) given over 90 minutes every 3 weeks until progression or prohibitive toxicity.

Guidelines

The National Comprehensive Cancer Network (NCCN) breast cancer guidelines (version 4.2020 – JMay 8, 2020) recommend trastuzumab in combination with chemotherapy and endocrine therapy for adjuvant treatment of HER2-positive breast cancer (category 1).^{2,5} Perjeta® (pertuzumab intravenous injection) can also be added to this treatment regimen (category 2A). 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.

The NCCN clinical practice guidelines on gastric cancer (version 2.2020 – May 13, 2020) and on esophageal and esophagogastric junction cancers (version 2.2020 – May 13, 2020) state that for metastatic or locally advanced disease (where local therapy is not indicated) trastuzumab should be added to first-line systemic chemotherapy for HER2-overexpressing adenocarcinoma.³⁻⁵ 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 2B) [various regimens based on individual patient variability]. Trastuzumab is not recommended for use in combination with anthracyclines.

Uterine serous carcinoma is a rare, aggressive histology of endometrial cancer. The NCCN guidelines for uterine neoplasms (version 1.2020 – March 6, 2020) lists the combination chemotherapy regimen of carboplatin/paclitaxel/trastuzumab as one of the recommended therapies for patients with HER2-positive uterine serous carcinoma (category 2A).⁶

The NCCN Compendium recommends use of trastuzumab for endometrial carcinoma and rectal or colon cancer.⁵

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of trastuzumab products. 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 a 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 trastuzumab products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of trastuzumab products is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Breast Cancer.** Approve if the patient meets the following criteria (A, B, and C):
 - A) The medication is prescribed by or in consultation with an oncologist; AND
 - B) The 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.

Dosing: Approve one of the following doses (A, B, or C):¹⁻²

- A) 4 mg per kg intravenous infusion followed by 2 mg per kg intravenous infusion not more frequently than once weekly; OR
- B) 8 mg per kg intravenous infusion followed by 6 mg per kg intravenous infusion not more frequently than once every 3 weeks; OR
- C) 4 mg per kg intravenous infusion followed by 2 mg per kg intravenous infusion not more frequently than once weekly during chemotherapy, followed by 6 mg per kg intravenous infusion not more frequently than once every 3 weeks.

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

- A) The medication is prescribed by or in consultation with an oncologist; AND
- B) Patient has human epidermal growth factor receptor 2 (HER2)-positive locally advanced or metastatic disease; AND
- C) Trastuzumab will be used first-line in combination with chemotherapy.
Note: Examples of chemotherapy are cisplatin, oxaliplatin, capecitabine, 5-fluorouracil [5-FU].

Dosing. Approve one of the following doses (A or B):^{1,5-6}

- A) 8 mg per kg intravenous infusion followed by 6 mg per kg intravenous infusion not more frequently than once every 3 weeks;^{1,4-6} OR
- B) 6 mg per kg intravenous infusion followed by 4 mg per kg intravenous infusion not more frequently than once every 2 weeks.⁵⁻⁶

Other Uses with Supportive Evidence

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

Dosing: Approve the following dose:

- A) Trastuzumab 8 mg per kg intravenous infusion followed by 6 mg per kg intravenous infusion not more frequently than once every 3 weeks.¹⁰

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- 4. Colon or Rectal Cancer.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
- A) The medication is prescribed by or in consultation with an oncologist; AND
 - B) The patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
 - C) The medication is used in combination with Perjeta[®] (pertuzumab for injection) or Tykerb[®] (lapatinib tablets).

Dosing: Approve up to 8 mg per kg intravenous infusion followed by up to 6 mg/kg intravenous infusion not more frequently than once every 3 weeks.^{7,8}

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Trastuzumab has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

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[®] for injection for intravenous use [prescribing information]. South San Francisco, CA: Genentech, Inc.; November 2018.
2. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 4.2020 – May 8, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on June 7, 2020.
3. The NCCN Gastric Clinical Practice Guidelines in Oncology (Version 2.2020 – May 13, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on June 7, 2020.
4. The NCCN Esophageal and Esophagogastric Junction Cancers Clinical Practice Guidelines in Oncology (Version 2.2020 – May 13, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on June 7, 2020.
5. The NCCN Drugs & Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on June 6, 2020. Search term: trastuzumab.
6. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (Version 1.2020 – March 6, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on June 7, 2020.
7. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 3.2020 – May 6, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on June 7, 2020.
8. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (Version 4.2020 – May 21, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on June 7, 2020.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual revision	Breast cancer criteria revised to replace neoadjuvant therapy with preoperative therapy. Oxaliplatin was added as an option for combination use with Herceptin in gastric or gastroesophageal junction cancer.	04/13/2016
Annual revision	No criteria changes	05/24/2017
Annual revision	Added new approval condition for endometrial carcinoma based on guidelines/compendium. Under Other Cancer Indications, deleted non-small cell lung cancer and added salivary gland tumor.	07/25/2018
Annual revision	<p>Breast Cancer: Changed file and policy name to Trastuzumab Products due to the inclusion of several biosimilars. Deleted Initial/Extended Approval, Duration of Therapy, Labs/Diagnostics, Waste Management, Other Cancer Indications, and Patient has been Started on Herceptin criteria. Added approval duration within criteria: for neoadjuvant/adjvant therapy, added approval for 1 year (total); for recurrent/metastatic disease, approval is for 1 year and can be continued yearly. Deleted criteria that Herceptin will be used as part of a taxane containing regimen, since in some cases it could be used as a single agent. Clarified dosing frequency to state “not more frequently than” the duration listed for each dosing.</p> <p>Gastric, Esophageal, or Gastroesophageal (GE) Junction Cancer. Added “Esophageal” to the condition approval. Specified that trastuzumab will be used “first-line” in combination with “chemotherapy” and the examples are listed as a Note. Because first-line has been added, deleted criteria that patient has not received prior therapy for metastatic disease. Clarified dosing frequency to state “not more frequently than” the duration listed for each dosing. Endometrial Carcinoma: Instead of listing specific agents, modified to state Trastuzumab will be used in combination with “chemotherapy” and listed the agents as examples in a Note. In Dosing section deleted “when used in combination with carboplatin/paclitaxel”. Instead, just listed trastuzumab dose and added “not more frequently than once” every 3 weeks.</p>	07/31/2019
Early annual revision	Added new condition of approval for Colon or Rectal Cancer based on guidelines.	06/10/2020