MEDICAL MUTUAL®

Drug Policy

Policy:	201404	Initial Effective Date:	04/28/2014
Code(s):	HCPCS J9355 and J9999	Annual Review Date:	07/19/2018
SUBJECT:	Herceptin® (Trastuzumab) Ogivri (trastuzumab-dkst)	Last Reviewed Date:	07/19/2018

Prior approval is required for some or all procedure codes listed in this Corporate Drug Policy.

OVERVIEW

Herceptin is 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] Herceptin is 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. Herceptin is a humanized monoclonal antibody that selectively binds with high affinity to the extracellular domain of the HER2 protein. The HER2 proto-oncogene encodes a transmembrane receptor protein which is structurally related to the epidermal growth factor receptor. Herceptin has been shown, in both *in vitro* assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2.

Herceptin is available as lyophilized powder in multi-use vials containing 440 mg per vial.[1] Herceptin should be reconstituted to a 21 mg/mL solution, which should be diluted. Dilute reconstituted Herceptin 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. Herceptin should not be administered as an intravenous push or bolus.

On Dec. 1, 2017, the U.S. Food and Drug Administration (FDA) approved Mylan and Biocon's Ogivri (trastuzumab-dkst), a biosimilar to Genentech's Herceptin® (trastuzumab). Ogivri was approved for both Herceptin-approved indications. It is indicated for treating patients with breast or metastatic stomach cancer (gastric or gastroesophageal junction adenocarcinoma) whose tumors overexpress the HER2 gene (HER2+). It is administered as an intravenous (IV) infusion. The dose of Ogivri varies depending on the indication.

Policy Statement

This policy involves the use of Herceptin or Ogivri. Prior approval is required for medical benefit coverage of Herceptin or Ogivri. Approval is recommended for those who meet the conditions of coverage in the **Criteria**, **Dosing**, **Initial/Extended Approval**, **Duration of Therapy**, and **Labs/Diagnostics** required for the diagnosis provided. The

requirement that the patient meet the Criteria for coverage of the requested medication applies to the initial authorization only. **Waste Management** applies for all covered conditions. Conditions Not Recommended for Approval are listed following the recommended authorization criteria and Waste Management section.

Because of the of the specialized skills required for evaluation and diagnosis of patients treated with Herceptin or Ogivri, as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Herceptin or Ogivri to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is allowed, a response to therapy is required for continuation of therapy.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Herceptin or Ogivri is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Breast Cancer.

Criteria. *The patient must meet the following criteria (A AND B)*:
A) Herceptin or Ogivri is prescribed by or in consultation with an oncologist; AND
B) Patient meets ONE of the following criteria (i or ii):
   i. Herceptin or Ogivri is being used for preoperative/adjuvant therapy and both of the following criteria are met (a and b):
      a) Patient has HER2-positive disease; AND
      b) Herceptin or Ogivri will be given as part of a taxane-containing regimen (e.g., paclitaxel or docetaxel); OR
   ii. Herceptin or Ogivri is being used for recurrent or metastatic HER2-positive disease.

Herceptin or Ogivri is indicated for 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) with docetaxel and carboplatin; or 3) as a single agent following multi-modality anthracycline- (e.g., daunorubicin, doxorubicin, epirubicin, idarubicin) based therapy.[1] Herceptin is also indicated in combination with paclitaxel for first-line treatment of HER2 overexpressing metastatic breast cancer, and as a single agent for treatment of HER2 overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

The National Comprehensive Cancer Network (NCCN) breast cancer guidelines (version 1.2016) indicate that for *preoperative/adjuvant treatment* of HER2-positive breast cancer, the preferred Herceptin-containing regimens include: doxorubicin/cyclophosphamide (AC) followed by paclitaxel (T) plus concurrent Herceptin with or without Perjeta® (pertuzumab intravenous injection); or docetaxel/carboplatin/Herceptin (TCH) with or without Perjeta.[2] Other Herceptin-containing preoperative/adjuvant regimens include: AC followed by docetaxel plus Herceptin with or without Perjeta; docetaxel/cyclophosphamide/Herceptin; 5-FU/epirubicin/cyclophosphamide (FEC) followed by docetaxel (or paclitaxel) plus Herceptin plus Perjeta; paclitaxel/Herceptin; or Herceptin plus Perjeta plus docetaxel (or paclitaxel) followed by FEC. Patients with HER2-positive tumors should be treated with preoperative systemic therapy including Herceptin for at least 9 weeks of preoperative therapy. A Perjeta-containing regimen may be given

preoperatively in certain patients with HER2-positive early stage breast cancer. 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 Herceptin plus docetaxel (category 1) or paclitaxel (category 2A). The guidelines also note that in the metastatic setting, patients previously treated with chemotherapy plus Herceptin without Perjeta may be considered for one line of therapy including both Herceptin plus Perjeta in combination with or without cytotoxic therapy (such as vinorelbine or a taxane). Other first-line regimens for HER2-positive recurrent or metastatic disease include Herceptin plus paclitaxel with or without carboplatin; Kadcyla® (ado-trastuzumab emtansine intravenous injection) alone; or Herceptin plus one of the following drugs: docetaxel, vinorelbine, or capecitabine. The preferred agents for *Herceptin-exposed HER2-positive recurrent or metastatic disease* include Tykerb® (lapatinib tablets) plus capecitabine; Herceptin plus capecitabine; Herceptin plus Tykerb (without cytotoxic therapy); or Herceptin plus other chemotherapy agents (i.e., carboplatin, cisplatin, cyclophosphamide, eribulin, gemcitabine, Ixempra® (ixabepilone intravenous injection), Abraxane® [paclitaxel albumin-bound for injectable suspension]). Several trials have shown benefit of continuing Herceptin therapy after disease progression on a Herceptin-containing regimen. However, the guidelines state that the optimal duration of Herceptin in patients with long-term control of disease is unknown.

The guidelines note that studies have confirmed that in the preoperative treatment of HER2-positive primary breast cancer, the use of HER2-targeted therapy (e.g., Herceptin) is important.[2]

The NCCN guidelines recommend, based on limited studies showing an improvement in progression free survival (PFS), that Tykerb or Herceptin be used in combination with aromatase inhibition for the treatment of recurrent or Stage IV ER-positive, HER2-positive breast cancer in postmenopausal women.[2] Men with breast cancer should be treated similarly to postmenopausal women, except that use of an aromatase inhibitor is ineffective without concomitant suppression of testicular steroidogenesis.

In the Phase III Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) trial, 8,381 patients with HER2-positive *early breast cancer* were randomized to 1 year of adjuvant therapy with Herceptin, Tykerb, the sequence of Herceptin to Tykerb (H → T), or the combination of Herceptin and Tykerb.[3] The Tykerb arm was closed early after the first interim analysis because the likelihood of showing non-inferiority to Herceptin was unlikely, and patients receiving Tykerb had a worse disease-free survival (DFS) than patients treated with Herceptin alone. In the intent-to-treat population there was a 16% reduction in the hazard of a DFS with Herceptin plus Tykerb compared with Herceptin, but this was not statistically significant and of minor clinical significance considering the additional toxicity with the combination. The authors concluded that 1 year of adjuvant Herceptin is the standard of care.

Breast cancer tumors are classified as HER2-positive if they demonstrate HER2 gene amplification by an *in situ* hybridization (ISH) method or are scored as 3+ by an immunohistochemistry (IHC) method.[2,4] Samples scored as 2+ by the IHC method are designated as equivocal (borderline) and should be subjected to reflex testing by an ISH method to assign HER2 status. Similarly, samples with equivocal results by an ISH assay must be confirmed by counting additional cells or repeating the ISH assay. If the results continue to be equivocal, then reflex testing with IHC is recommended to assign HER2 status.

Dosing in Breast Cancer. *Dosing must meet ONE of the following (A OR B OR C):*[1-2]

A) 4 mg per kg intravenous infusion followed by 2 mg per kg intravenous infusion weekly; OR

B) 8 mg per kg intravenous infusion followed by 6 mg per kg intravenous infusion every 3 weeks; OR

C) 4 mg per kg intravenous infusion followed by 2 mg per kg intravenous infusion weekly during chemotherapy, followed by 6 mg per kg intravenous infusion every 3 weeks.

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.

Permanently discontinue Herceptin for severe or life-threatening infusion-related reactions, or for a persistent (more than 8 weeks) left ventricular ejection fraction (LVEF) decline or for suspension of Herceptin dosing on more than three occasions for cardiomyopathy.

Note: Dose modifications are recommended for the management of infusion reactions and cardiomyopathy, and are determined by the prescribing physician. See the prescribing information for more detail.

Initial Approval/Extended Approval.

A) Preoperative/adjuvant therapy:
   i. Initial Approval: Approve 12 months of therapy.
   ii. Extended Approval: Approve 12 months of therapy.

B) Recurrent or metastatic disease.
   i. Initial Approval: Initial approval is for 6 months of therapy.
   ii. Extended Approval: Approve at additional 6 month intervals, as determined by the prescribing physician.

Duration of therapy in Breast Cancer.

A) For preoperative/adjuvant treatment: up to 52 weeks.

B) For metastatic treatment: indefinite.

Labs/Diagnostics. Detection of HER2 protein overexpression or gene amplification is necessary for selection of patients appropriate for Herceptin or Ogivri therapy. See criteria above.

Either an IHC test or an ISH test has been determined to be an acceptable method for making an initial determination of HER2 tumor status in breast cancer.[2,4]

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2. <u>Gastric or Gastroesophageal (GE) Junction Cancer</u>.

Criteria. *<u>The patient must meet the following criteria (A, B, C, AND D)</u>*:

A) Herceptin or Ogivri is prescribed by or in consultation with an oncologist; AND

B) Patient has HER2-positive locally advanced or metastatic disease; AND

C) Herceptin or Ogivri will be used in combination with cisplatin or oxaliplatin AND a fluoropyrimidine (capecitabine or 5-fluorouracil [5-FU]); AND

D) Patient has not received prior treatment for metastatic disease.

Herceptin or Ogivri is indicated, in combination with cisplatin and capecitabine or 5-FU, for the treatment of patients with HER2-overexpressing metastatic gastric or GE junction adenocarcinoma, who have not received prior treatment for metastatic disease.[1] In the pivotal, open-label, Phase III study (Trastuzumab for Gastric Cancer [ToGA] study), eligible patients had inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the stomach or GE junction with overexpression of HER2 (i.e., HER2-positive).[5] Patients (n = 594) were randomized to treatment with chemotherapy that included capecitabine plus cisplatin or 5-FU plus cisplatin given every 3 weeks for 6 cycles or to chemotherapy in combination with Herceptin. Patients continued on therapy with Herceptin until disease progression, unacceptable toxicity, or withdrawal of consent. Median overall survival (OS) was 13.8 months with Herceptin plus chemotherapy (95% confidence interval [CI]: 12, 16) and 11.1 months with chemotherapy alone (95% CI: 10, 13) [hazard ratio (HR) 0.74; 95% CI: 0.60, 0.91; P = 0.0046]. In a post hoc subgroup analysis of patients who received Herceptin plus chemotherapy, median OS was 16.0 months (95% CI: 15, 19) in patients with high expression of HER2 protein vs. 11.8 months (95% CI: 10, 13) in patients with low expression of HER2 protein. The HR for patient whose tumors had high HER2 expression was 0.65 (95% CI: 0.51, 0.83). In one multicenter Phase II trial, patients with HER2-positive advanced gastric cancer (n = 55) were given Herceptin in combination with capecitabine and oxaliplatin.[6] The objective response rate was 68% (95% CI: 54%, 80%). The disease control rate defined as the proportion of patients demonstrating complete responses, partial responses, or stable disease was 89% (95% CI: 78%, 95%). After a median follow-up period of 13.8 months (range, 6.1 to 23.9), the median PFS was 9.8 months (95% CI: 7.0,12.6) and OS was 21.0 months (95% CI: 6.4, 35.7).

The NCCN clinical practice guidelines on gastric cancer (version 1.2016) and on esophageal and GE junction cancer (version 3.2015) state that for metastatic or locally advanced disease (where local therapy is not indicated) Herceptin should be added to first-line systemic chemotherapy for HER2-neu overexpressing adenocarcinoma in patients with Karnofsky performance score ≥ 60% or Eastern Cooperative Oncology Group (ECOG) performance score ≤ 2.[7-8] The recommended regimens for metastatic or locally advanced HER2-positive gastric, esophageal, or esophagogastric junction adenocarcinoma are Herceptin in combination with cisplatin (or oxaliplatin) and a fluoropyrimidine (5-FU or capecitabine) [category 1] or Herceptin in combination with other chemotherapy agents (category 2B) [various regimens based on individual patient variability]. Herceptin is not recommended for use in combination with anthracyclines.

Dosing in Metastatic Gastric or Gastroesophagel (GE) Junction Cancer. *Dosing must meet the following (A OR B):*[1,7]

A) 8 mg per kg intravenous infusion followed by 6 mg per kg intravenous infusion every 3 weeks;[1,5,7-8] OR

B) 6 mg per kg intravenous infusion followed by 4 mg per kg intravenous infusion every 2 weeks.[7]

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.[7-8]

Permanently discontinue Herceptin for severe or life-threatening infusion-related reactions, or for a persistent (more than 8 weeks) LVEF decline or for suspension of Herceptin dosing on more than three occasions for cardiomyopathy.[1]

Note: Dose modifications are recommended for the management of infusion reactions and cardiomyopathy, and are determined by the prescribing physician. See the prescribing information for more detail.

Initial Approval/Extended Approval.

A) *Initial Approval:* Initial approval is for 6 months of therapy.

B) *Extended Approval:* Approve at additional 6-month intervals if the patient does not have disease progression, as determined by the prescribing physician.

Duration of Therapy in Gastric or Gastroesophagel (GE) Junction Cancer. Indefinite if the patient does not have disease progression.

Labs/Diagnostics. Detection of HER2 protein overexpression or gene amplification is necessary for selection of patients appropriate for Herceptin therapy. See criteria above.

NCCN guidelines recommend assessment for tumor HER2-neu overexpression using IHC and fluorescence in situ hybridization (FISH) or other *in situ* hybridization method (i.e., ISH).[5,8]

Other Uses with Supportive Evidence

3. Patient has been Started on Herceptin or Ogivri.

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

A) The patient has HER2-positive breast, gastric, or gastroesophageal (GE) junction cancer; AND

B) The patient meets the conditions for coverage required for **Dosing**, **Extended Approval**, **Duration of Therapy**, and **Labs/Diagnostics** for an approved use in this *Herceptin or Ogivri Utilization Review* policy.

Treatment guidelines for breast cancer indicate that patients with tumors IHC 0 or 1+ for HER2 or ISH not amplified (i.e., HER2-negative) have very low rates of HER2-targeted response, and therapy with Herceptin is not warranted. Treatment guidelines indicate that HER2-tumor status should be determined for all newly diagnosed invasive breast cancers and for first recurrences of breast cancer whenever possible if previously unknown or negative.[2,4] Despite concerns regarding accuracy of HER2 assays in clinical practice, either an IHC or ISH test has been determined to be an acceptable method for making an initial determination of HER2 tumor status.

The NCCN guidelines note that the most important clinical application of HER2 status in patients with gastric cancer concerns the management of patients with advanced or metastatic disease.[7] The scoring system for breast cancer differs from that used for gastric or GE junction cancer.[7-8] For patients with inoperable locally advanced, recurrent or metastatic adenocarcinoma of the stomach or GE junction for whom Herceptin therapy is being considered, NCCN guidelines recommend assessment for tumor HER2-neu overexpression using IHC, and if results are equivocal, then confirmed with FISH or other *in situ* hybridization method. The NCCN guidelines panel recommends that cases showing 2+ expression of HER2-neu by IHC should be additionally examined by FISH or other ISH methods. Tumors with 3+ overexpression by IHC or with IHC 2+ and FISH positive (HER2:CEP17 ratio $\geq$ 2) are considered positive. (Some institutions routinely perform both IHC and FISH on all patients.) In a post-hoc sub group analysis of the ToGA trial, the addition of Herceptin to chemotherapy improved OS in patients whose tumors were IHC 2+ and FISH positive or IHC 3+ when compared to patients whose tumors were IHC 0 or 1+ and FISH positive.[5,7-8]

4. Other Cancer Indications. Forward to the Medical Director for review on a case-by-case basis. Other indications supported in the *NCCN Compendium*[9] include: leptomeningeal metastases from breast cancer (category 2A) [intrathecal route] and non-small cell lung cancer (category 2B).

Waste Management for All Indications.

- Weight-based dosing is used; the dose should be calculated and the number of vials needed assessed.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Herceptin or Ogivri have 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. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

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

Documentation Requirements:

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

HCPCS Code J9355 and J9999 †requires prior approval.

†When *unclassified antineoplastic* (J9999) is determined to be Ogivri

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HCPCS Code(s):	
J9355	Injection, trastuzumab, 10 mg
J9999	Unclassified antineoplastic