BlueCross BlueShield of North Carolina

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Corporate Medical Policy

Trastuzumab (Herceptin®) and Trastuzumab Biosimilars

File Name:	trastuzumab_herceptin_and_trastuzumab_biosimilars
Origination:	2/1999
Last CAP Review:	3/2020
Next CAP Review:	3/2021
Last Review:	10/2020

Description of Procedure or Service

In certain cancers, the human epidermal growth factor receptor 2 (HER2) gene is amplified and overexpressed. Trastuzumab (Herceptin) is a humanized monoclonal antibody, HER2 protein receptor antagonist, which may be used for the treatment of certain cancers that overexpress HER2. This policy addresses trastuzumab, trastuzumab and hyaluronidase combination, and trastuzumab biosimilars.

Approximately 20% to 25% of breast cancers overexpress *HER2*, a transmembrane glycoprotein receptor with tyrosine kinase activity. *HER2*, previously called HER2/neu, or ErbB-2,6 is part of the HER tyrosine kinase receptor family that includes 4 transmembrane receptors (*HER1* [also known as epidermal growth factor receptor, *HER2, HER3, HER4*). These receptors mediate tumor cell growth, survival, and differentiation. Human epidermal growth factor receptors, when activated by extracellular ligand binding, dimerize and activate cell-signaling through the phosphatidyl inositol-3 (PI3)-kinase/AKT pathway, which regulates tumor cell survival, and the mitogen-activated protein kinase pathway, which regulates cellular proliferation. *HER2* has no known ligand; it forms active heterodimers (particularly *HER2*:*HER3*) and, when overexpressed, homodimers (*HER2*:*HER2*) that constitutively activate tyrosine kinase signaling.

HER2 overexpression is associated with reduced time to disease recurrence and poorer prognosis. Before the advent of *HER2*-targeted therapy, *HER2* overexpression was associated with shorter disease-free and overall survival than either lymph node–negative or lymph node–positive breast cancers; with lack of responsiveness to tamoxifen therapy; and with altered responsiveness to cytotoxic chemotherapy.

Treatment of *HER2*-Positive Breast Cancer
The Food and Drug Administration (FDA) has approved multiple anti-*HER2* therapies. These agents arrest tumor cell growth and promote apoptosis by blocking *HER2*-mediated intracellular-signaling pathways that mediate cell growth, differentiation, and survival:

- Trastuzumab (Herceptin) is an intravenous monoclonal antibody to an extracellular domain of the *HER2* receptor (subdomain IV) that prevents activation of intracellular tyrosine kinase signaling cascades and also promotes antibody-dependent cell-mediated cytotoxicity.
- Lapatinib (Tykerb®) is an oral tyrosine kinase inhibitor that blocks the intracellular tyrosine kinase domain of *HER2* and downstream cell-signaling cascades.
- Pertuzumab (Perjeta™) is an intravenous monoclonal antibody to the extracellular dimerization domain of the *HER2* receptor (subdomain II) that, like trastuzumab, prevents activation of intracellular tyrosine kinase signaling cascades and also promotes antibody-dependent cell-mediated cytotoxicity.
- Ado-trastuzumab emtansine (Kadcyla™) is an intravenous antibody-drug conjugate of trastuzumab and emtansine.

- Neratinib (Nerlynx®) is an oral kinase inhibitor that reduces *HER* autophosphorylation by irreversibly binding to *HER2*, Neratinib is indicated for the extended adjuvant treatment for early *HER2*-over expressed breast cancer.
- Trastuzumab and hyaluronidase-oysk (Herceptin Hylecta™) is a subcutaneous combination drug that contains trastuzumab and hyaluronidase. Hyaluronidase has been shown to increase the absorption rate of trastuzumab into systemic circulation.

Lapatinib, pertuzumab, ado-trastuzumab emtansine, and neratinib are each addressed separately in individual policies as referenced below.

Trastuzumab is recommended as first-line treatment for patients with *HER2*-positive metastatic breast cancer, either in combination with pertuzumab and a taxane (preferred); in combination with a taxane (paclitaxel with or without carboplatin, or docetaxel), vinorelbine, or capecitabine; or as monotherapy. Treatment with trastuzumab plus an anthracycline (doxorubicin or daunorubicin) is not recommended because of unacceptably high rates of cardiac toxicity. Most patients who initially respond to trastuzumab will eventually progress.

For second-line treatment of *HER2*-positive metastatic breast cancer that progresses after trastuzumab therapy (either in the adjuvant setting or as first-line treatment for metastatic disease), a continuation of the *HER2* blockade is recommended. For patients not previously exposed to pertuzumab, combination therapy with trastuzumab plus pertuzumab with or without cytotoxic chemotherapy (eg, a taxane or vinorelbine) is recommended. Other treatment options are trastuzumab plus lapatinib or capecitabine and lapatinib plus capecitabine. In patients who obtain sustained disease control, the optimal duration of *HER2*-targeted therapy is unknown.

Regulatory Status

Trastuzumab (Herceptin®) is a humanized monoclonal antibody against the extracellular domain of *HER2*. Trastuzumab has received FDA marketing approval for treatment of *HER2*-positive breast cancer in both the adjuvant and metastatic settings, and metastatic gastric or gastroesophageal junction adenocarcinoma. It first received FDA approval in September 1998 for use in metastatic breast cancer, as a first-line therapy in combination with paclitaxel and as a single agent in second- and third-line therapy.

The current FDA-approved labeling, as of September 2016, states that trastuzumab is indicated as follows:

1. For *adjuvant* treatment of *HER2* overexpressing node-positive or node-negative (ER/PR negative or with one high-risk feature) *breast cancer*:
   - as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel;
   - as part of a treatment regimen of docetaxel and carboplatin; or
   - as a single agent following multi-modality anthracycline-based therapy.

   Trastuzumab is administered by IV (intravenous) infusion weekly or every 3 weeks for a total of 52 weeks depending on the dosing schedule and chemotherapy used for adjuvant treatment.

2. For treatment of *HER2* overexpressing *metastatic breast cancer* 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. Trastuzumab is administered by IV infusion weekly until disease progression.

3. For treatment of *HER2* overexpressing *metastatic gastric or gastroesophageal junction adenocarcinoma*, in combination with cisplatin and capecitabine or 5-fluorouracil, in patients

who have not received prior treatment for metastatic disease. Trastuzumab is administered by IV infusion every 3 weeks until disease progression.

While trastuzumab has the FDA approval for breast cancer in specific settings and for gastric or gastroesophageal junction adenocarcinoma, its use has been investigated in the preoperative (neoadjuvant) setting for breast cancer, in combination with regimens besides those specified in the FDA-approved product label, and in a wide range of other types of cancer that overexpress *HER2*.

Trastuzumab carries a black box warning for cardiomyopathy, infusion reactions, and embryo-fetal toxicity. The prescribing labels state that patients should be evaluated for cardiac function before and during treatment as well as use effective contraception prior and during treatment.

The following biosimilars for trastuzumab have been approved by the FDA for the same labeled indications as the parent drug, Herceptin (trastuzumab), for the treatment of *HER2* overexpressing breast cancer and the treatment of *HER2* overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma:

- December 2017, Ogivri (trastuzumab-dkst; Mylan)
- December 2018, Herzuma (trastuzumab-pkrb; Teva)
- January 2019, Ontruzant (trastuzumab-dttb; Merck)
- March 2019, Trazimera (trastuzumab-qyyp; Pfizer)
- June 2019, Kanjinti (trastuzumab-anns; Amgen)

In February 2019, Herceptin Hylecta (trastuzumab and hyaluronidase-oysk) was approved by the FDA for the same labeled indications as trastuzumab for the treatment of *HER2* overexpressing breast cancer.

Related Medical Policies:
Pertuzumab for Treatment of Malignancies
Ado-Trastuzumab Emtansine (Trastuzumab-DM1) for Treatment of HER-2 Positive Malignancies

Related Pharmacy Policies:
Tykerb® (Lapatinib)
Nerlynx®

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for trastuzumab, trastuzumab and hyaluronidase-oysk, and trastuzumab biosimilars (trastuzumab-dkst, trastuzumab-pkrb, trastuzumab-dttb, trastuzumab-qyyp, trastuzumab-anns) when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Trastuzumab is covered

***HER2*-positive Breast Cancer**

Trastuzumab, trastuzumab and hyaluronidase-oysk, and trastuzumab biosimilars (trastuzumab-dkst, trastuzumab-pkrb, trastuzumab-dttb, trastuzumab-qyyp, trastuzumab-anns) may be considered medically necessary for the treatment of patients with breast cancer whose tumors overexpress the *HER2* protein (*HER2*-positive breast cancer). This includes use as adjuvant therapy, neoadjuvant therapy, and treatment of metastatic disease.

Conditions Other Than *HER2*-positive Breast Cancer

Trastuzumab and trastuzumab biosimilars (trastuzumab-dkst, trastuzumab-pkrb, trastuzumab-dttb, trastuzumab-qyyp, trastuzumab-anns) may be considered medically necessary, when used in combination with systemic chemotherapy, for treatment of patients with advanced (locally advanced or metastatic) gastric cancer or gastroesophageal junction adenocarcinoma whose tumors overexpress the *HER2* protein (*HER2*-positive cancer).

Trastuzumab may be considered medically necessary for treatment of patients with esophageal adenocarcinoma (not squamous or upper esophageal cancer) with clearly positive *HER2* overexpression, Category 1 when used with cisplatin and 5FU or capecitabine, and Category 2B with other combinations.

HER2-positive cancer is defined by patients who have tumors with *HER2* protein overexpression as per at least one of the following:

1. Immunohistochemistry (IHC) 3+; **or**
2. Fluorescent in situ hybridization (FISH) *HER2* gene copy is greater than 6; **or**
3. FISH ratio of *HER2* gene/chromosome 17 ratio is greater than or equal to 2.0.

AND

Trastuzumab (Hereptin) and trastuzumab biosimilars (trastuzumab-dkst, trastuzumab-pkrb, trastuzumab-dttb, trastuzumab-qyyp, trastuzumab-anns) may be considered medically necessary when the following criteria are met:

1. If the request is for trastuzumab (Herceptin) or non-preferred trastuzumab biosimilars, then both of the following criteria are met:
    a. The patient has a documented serious adverse event that required medical intervention to both preferred trastuzumab biosimilar products [trastuzumab-anns (Kanjinti), trastuzumab-dkst (Ogivri)] that is not anticipated with the requested product; **AND**
    b. The prescriber has completed and submitted an FDA MedWatch Adverse Event Reporting Form; **AND**

Use of trastuzumab, trastuzumab hyaluronidase-oysk, and trastuzumab biosimilars (trastuzumab-dkst, trastuzumab-pkrb, trastuzumab-dttb, trastuzumab-qyyp, trastuzumab-anns) may be considered medically necessary for clinical indications not listed above when the drug is prescribed for the treatment of cancer either:

- In accordance with FDA label (when clinical benefit has been established, see Policy Guidelines); **OR**
- In accordance with specific strong endorsement or support by nationally recognized compendia, when such recommendation is based on strong/high levels of evidence, and/or uniform consensus of clinical appropriateness has been reached.

When Trastuzumab is not covered

Except as noted above, trastuzumab, trastuzumab and hyaluronidase-oysk, and trastuzumab biosimilars (trastuzumab-dkst, trastuzumab-pkrb, trastuzumab-dttb, trastuzumab-qyyp, trastuzumab-anns) are considered **investigational** for the treatment of all other conditions including, but not limited to:

- *HER2*-negative breast cancer; and
- *HER2*-positive cancers except as outlined above in "When Trastuzumab is covered."

Trastuzumab, trastuzumab and hyaluronidase-oysk, and trastuzumab biosimilars (trastuzumab-dkst, trastuzumab-pkrb, trastuzumab-dttb, trastuzumab-qyyp, trastuzumab-anns) are considered investigational when used for:

1. Non-cancer indications; **OR**
2. When criteria are not met regarding FDA labeling **OR** strong endorsement/support by nationally recognized compendia, as stated under "When Trastuzumab is covered."

Policy Guidelines

Targeted anti-*HER2* therapy with trastuzumab has shown survival benefit for primary and metastatic breast cancer patients and has become the accepted and usual therapy for patients with *HER2*-positive breast cancer.

For individuals who have *HER2* overexpressing breast cancer who receive trastuzumab as adjuvant, neoadjuvant, or treatment of metastatic disease, the evidence includes randomized controlled trials, single-arm trials and meta-analysis. Relevant outcomes are overall survival, disease-specific survival, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. Trastuzumab has shown survival benefit for primary and metastatic breast cancer patients and has become the accepted and usual therapy for patients with *HER2* positive breast cancer. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have *HER2* overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who receive trastuzumab plus cisplatin and capecitabine or 5-fluorouracil, the evidence includes randomized controlled trial and single arm trial. Relevant outcomes are overall survival, disease-specific survival, morbid events, functional outcomes, health status measures, quality of life, treatment-related mortality and treatment-related morbidity. Trastuzumab has shown survival benefit for *HER2* overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma in one phase 3 trial that reported a 2-month overall survival benefit in the trastuzumab arm and no difference in server adverse events between the group that received chemotherapy plus trastuzumab versus chemotherapy alone. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have *HER2*-overexpressing malignancies (besides breast or gastric cancer) who are treated with trastuzumab plus standard of care, the evidence includes multiple single-arm and RCTs. Relevant outcomes are overall survival, disease-specific survival, morbid events, functional outcomes, health status measures, quality of life, treatment-related mortality and morbidity. The majority of these trials were conducted 10 to 15 years ago as pilots with small sample sizes in the early clinical development of trastuzumab. It should be noted that these trials ultimately reported negative or less than optimal efficacy results and they were terminated early due to limited accrual. The evidence is insufficient to determine the effects of technology on health outcomes.

Drugs prescribed for treatment of cancer in accordance with FDA label may be considered medically necessary when clinical benefit has been established, and should not be determined to be investigational as defined in Corporate Medical Policy (CMP), "Investigational (Experimental) Services."

Please refer to CMP "Investigational (Experimental) Services" for a summary of evidence standards

from nationally recognized compendia.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: *C9399, J3490, J3590, J9355, J9356, Q5112, Q5113, Q5114, Q5116, Q5117, S0353, S0354*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Herceptin

Genetech BioOncology product information

Blue Cross Blue Shield Association, Clearinghouse Update, September 1998, pp 1,3.

Oncology Consultant Review 11/98

Pegram MD, Lipton A. Phase II study of receptor-enhanced chemosensitivity using recumbent humanized anti-p185HER2/Neu monoclonal antibody plus cisplatin in patients with HER2/Neu overexpressing metastatic breast cancer refractory to chemotherapy treatment. J Clin Oncol. 1998; 16(8);2659-71.

Baselga J, Norton L. Recumbent humanized anti-HER2 antibody (Herceptin) enhances the antitumor activity of Paclitaxel and doxorubicin against HER2/neu overexpressing human breast cancer xenografts. Cancer Res. 1998; 58(13);2825-31.

Medical Policy Advisory Group 3/1/99

USPDI - 1999 - On-line Update Version - Developed 12/11/98 - 9/99

USPDI - 2000 - On-line Update Version - Developed 12/11/98. Revised 07/24/2000

Specialty Matched Consultant Advisory Panel - 6/2001

BCBSA Medical Policy Reference Manual, 12/18/02; 5.01.12

Specialty Matched Consultant Advisory Panel - 6/2003

National Institute for Clinical Excellence (NCCN). (2002). Guidance on the use of trastuzumab for the treatment of advanced breast cancer. Retrieved 2/9/2005 from http://www.nice.org.uk/page.aspx?o=29280.

BCBSA Medical Policy Reference Manual [Electronic Version], 5.01.12, 11/9/2004

Specialty Matched Consultant Advisory Panel - 4/2005

BCBSA Medical Policy Reference Manual [Electronic Version], 5.01.12, 12/14/2005

Specialty Matched Consultant Advisory Panel - 4/2007

BCBSA Medical Policy Reference Manual [Electronic Version], 5.01.12, 12/11/08

Specialty Matched Consultant Advisory Panel - 4/2009

BCBSA Medical Policy Reference Manual [Electronic Version], 5.01.12, 4/8/2010

Medical Director – 8/2010

Specialty Matched Consultant Advisory Panel – 3/2011

BCBSA Medical Policy Reference Manual [Electronic Version], 5.01.12, 4/14/2011

Trastuzumab

Specialty Matched Consultant Advisory Panel – 3/2012

BCBSA Medical Policy Reference Manual [Electronic Version], 5.01.12, 4/12/2012

Specialty Matched Consultant Advisory Panel – 3/2013

Specialty Matched Consultant Advisory Panel – 3/2014

BCBSA Medical Policy Reference Manual [Electronic Version], 5.01.12, 3/13/2014

BCBSA Medical Policy Reference Manual [Electronic Version], 5.01.12, 3/12/2015

Specialty Matched Consultant Advisory Panel- 3/2015

Medical director review 5/2015

BCBSA Medical Policy Reference Manual [Electronic Version], 5.01.12, 12/15/2015

Specialty Matched Consultant Advisory Panel- 3/2016

Medical Director review 8/2016

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Esophageal and Esophagogastric Junction Cancers, version 2.2016. Available online at: https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf

BCBSA Medical Policy Reference Manual [Electronic Version], 5.01.12, 10/13/2016

Specialty Matched Consultant Advisory Panel- 3/2017

BCBSA Medical Policy Reference Manual [Electronic Version], 5.01.12, 7/13/2017

Specialty Matched Consultant Advisory Panel- 3/2018

BCBSA Medical Policy Reference Manual [Electronic Version], 5.01.12, 8/9/2018

Specialty Matched Consultant Advisory Panel- 3/2019

BCBSA Medical Policy Reference Manual [Electronic Version], 5.01.12, 8/8/2019

Amgen Inc. Kanjinti (trastuzumab-anns) for injection for intravenous use. Highlights of prescribing information. June 2019. Available at: https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/kanjinti/kanjinti_pi.ashx. Last accessed September 2019.

Medical Director review 9/2019

Mylan Institutional LLC. Ogivri (trastuzumab-dkst) for injection, for intravenous use. Highlights of prescribing information. April 2019. Available at: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?type=display&setid=6b7938e6-14c7-4a65-9605-967542ecfb8f. Last accessed October 2019.

Teva Pharmaceuticals USA, Inc. Herzuma (trastuzumab-pkrb) for injection, for intravenous use. Highlights of prescribing information. May 2019. Available at: https://www.herzuma.com/globalassets/herzuma/herzuma-pi.pdf. Last accessed October 2019.

Merck & Co., Inc. Ontruzant (trastuzumab-dttb) for injection, for intravenous use. Highlights of prescribing information. January 2019. Available at: https://www.merck.com/product/usa/pi_circulars/o/ontruzant/ontruzant_pi.pdf. Last accessed October 2019.

Pfizer Inc. Trazimera (trastuzumab-qyyp) for injection, for intravenous use. Highlights of prescribing information. March 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761081s000lbl.pdf. Last accessed October 2019.

Medical Director review 10/2019

Genentech, Inc. Herceptin Hylecta (trastuzumab and hyaluronidase-oysk) injection, for subcutaneous use. Highlights of prescribing information. February 2019. Available at: https://www.gene.com/download/pdf/herceptin_hylecta_prescribing.pdf. Last accessed December 2019.

Medical Director review 12/2019

Specialty Matched Consultant Advisory Panel- 3/2020

Medical Director review 10/2020

Policy Implementation/Update Information

For Policy Titled: "Herceptin"

2/99	Original policy developed. There appears to be little benefit in using Herceptin with 2+HER2 overexpressors. At the same time, the test for overexpression is somewhat subjective.
5/99	Reformatted, description of service changed, medical terms added.
9/99	Revised to include 2+ HER2 overexpression as per 1999 USPDI on-line update information.

1/00 Revised to add new HCPCS code J9355.

3/01 System changes.

6/01 Specialty Matched Consultant Advisory Panel review. No change in criteria.

6/03 Specialty Matched Consultant Advisory Panel review. No criteria changes. Format changes.

4/04 Benefits Application and Billing/Coding sections updated for consistency.

5/5/05 Specialty Matched Consultant Advisory Panel meeting 4/14/2005. No changes to criteria. References added.

9/18/06 Medical Policy changed to Evidence Based Guideline.

5/21/07 Specialty Matched Consultant Advisory Panel review 4/25/2007. Added additional indication under "Evidence Based Guideline for Herceptin" which states; "Herceptin® in combination with adjuvant chemotherapy may be appropriate for patients who have had completely resected HER-2-positive breast cancer and have either of the following: 1. Node-positive disease; or 2. High-risk breast cancer, defined as either tumors greater than 1 cm if the tumor is estrogen receptor negative OR if the tumor is greater than 2 cm and is estrogen receptor positive." References added.

5/18/09 The following statement was added to the guideline: "Herceptin as a component of preoperative (neoadjuvant or primary systemic) therapy, followed by additional postoperative adjuvant trastuzumab may be appropriate to complete a full year of treatment, for patients with HER2-positive breast cancer undergoing medically appropriate preoperative chemotherapy." Also added a statement to indicate Herceptin may not be appropriate for indications other than those listed in the guideline, including the treatment of other malignancies such as osteosarcoma, non-small-cell lung, ovarian, prostate, head and neck, esophageal, gastric, pancreatic, colorectal, endometrial, or urothelial cancers. Specialty Matched Consultant Advisory Panel review 4/21/09. (btw)

6/22/10 Policy Guideline Number(s) removed (amw)

9/14/10 "Description" section extensively revised. Reworded the "When Recommended" section to indicate; "Trastuzumab may be appropriate, when used in combination with systemic chemotherapy, for treatment of patients with advanced (locally advanced or metastatic) gastric cancer or gastroesophageal junction adenocarcinoma whose tumors overexpress the HER2 protein (HER2-positive cancer). " The "When Not Recommended" section reworded to remove reference to gastric cancer and gastroesophageal adenocarcinoma. Medical Director review 8/10/2010. References added. (btw)

4/26/11 Specialty Matched Consultant Advisory Panel review March 30, 2011. No changes made to guideline. (btw)

6/21/11 Reference added. (btw)

For Policy Re-titled: "Trastuzumab"

5/1/12 Title changed from "***Herceptin***" to "***Trastuzumab***". Specialty Matched Consultant Advisory Panel review 3/21/2012. Removed "esophageal and gastric" from the When Not Recommended section. No change to guideline intent. (btw)

6/29/12 Description section revised. No change to guideline intent. Policy Guidelines updated. Medical Director review 6/10/12. Reference added. (btw)

4/16/12 Specialty Matched Consultant Advisory Panel review 3/20/2013. Added "esophageal (except as noted above), gastric (except as noted above)" to the When Not Recommended statement. (btw)

4/15/14 Specialty Matched Consultant Advisory Panel review 3/25/2014. No changes made to guideline. (btw)

5/13/14 Reference added. (btw)

5/26/15 Evidence based guideline converted to corporate medical policy. Medical director review. Specialty matched consultant advisory panel review 3/2015. Reference added. Notification given 5/26/15 for effective date 7/28/15. (lpr)

11/24/15 Reference added. No change to policy statement. (lpr)

4/29/16 Specialty Matched Consultant Advisory Panel review 3/30/2016. No change to policy intent. (lpr)

12/30/16 Added definition of HER2 in the "When Covered" section. Added covered indication for esophageal adenocarcinoma: "Trastuzumab may be considered medically necessary for treatment of patients with esophageal adenocarcinoma (not squamous or upper esophageal cancer) with clearly positive HER2 overexpression, Category 1 when used with Cisplatin and 5FU or Capecitabine, and Category 2B with other combinations." Added HCPCS codes S0353 and S0354 to Billing/Coding section. Updated Policy Guidelines section. Medical Director review 10/2016. Reference added. Notification given 12/30/16 for effective date 4/1/17. (lpr)

4/28/17 Added the following statement to "When Covered" section: "Use of Trastuzumab may be considered medically necessary for clinical indications not listed above when the drug is prescribed for the treatment of cancer either: In accordance with FDA label (when clinical benefit has been established, see Policy Guidelines); OR In accordance with specific strong endorsement or support by nationally recognized compendia, when such recommendation is based on strong/high levels of evidence, and/or uniform consensus of clinical appropriateness has been reached". Under "When Not Covered" section, added the statement "Trastuzumab is considered investigational when used for: 1)Non-cancer indications; **OR** 2) When criteria are not met regarding FDA labeling **OR** strong endorsement/ support by nationally recognized compendia, as stated under "When Trastuzumab is covered." Added the following statements under "Policy Guidelines" section: 1)Drugs prescribed for treatment of cancer in accordance with FDA label may be considered medically necessary when clinical benefit has been established, and should not be determined to be investigational as defined in Corporate Medical Policy, Investigational (Experimental) Services." 2) Please refer to CMP "Investigational (Experimental) Services" for a summary of evidence standards from nationally recognized compendia. Medical director review 3/2017. Specialty Matched Consultant Advisory Panel review 3/29/17. No change to policy statement. (lpr)

8/25/17 Updated Description and Policy Guidelines sections. No change to policy statement. Reference added. (lpr)

4/27/18 Specialty Matched Consultant Advisory Panel review 3/2018. No change to policy intent. (krc)

10/26/18 Reference added. (krc)

4/16/19 Specialty Matched Consultant Advisory Panel review 3/20/2019. No change to policy statement. (krc)

10/1/19 Under "When Covered," added Kanjinti (trastuzumab-anns) biosimilar to Herceptin (trastuzumab) for the treatment of *HER2* overexpressing breast cancer and *HER2* overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. Added reference to related policies for Perjeta, Kadcyla, and Tykerb. Added HCPCS codes Q5117, C9399, J3490, J3590 to Billing/Coding section effective 10/1/19. References added. Medical Director review 9/2019. (krc)

10/29/19 Under "When Covered," added Ogivri (trastuzumab-dkst), Herzuma (trastuzumab-pkrb), Ontruzant (trastuzumab-dttb), and Trazimera (trastuzumab-qyyp) biosimilars to Herceptin (trastuzumab) for the treatment of *HER2* overexpressing breast cancer and *HER2* overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. Added HCPCS codes Q5112, Q5113, Q5114, and Q5116 to Billing/Coding section. References added. Medical Director review 10/2019. **Notification given 10/29/2019 for effective date 12/31/2019**. (krc)

12/31/19 Under "When Covered," added Herceptin Hylecta (trastuzumab and hyaluronidase-oysk) for the treatment of *HER2* overexpressing breast cancer indications. Reformatted "When Not Covered" section for clarity, with no change to intent. Updated Description section to reflect addition of Herceptin Hylecta to policy. Added reference to related policy for Nerlynx. Added HCPCS code J9356 to Billing/Coding section. References added. Medical Director review 12/2019. **Notification given 12/31/2019 for effective date 4/1/2020**. (krc)

For Policy Re-titled: "Trastuzumab (Herceptin®) and Trastuzumab Biosimilars"

3/31/20 Policy title changed from ***Trastuzumab*** to ***Trastuzumab (Herceptin®) and Trastuzumab Biosimilars***. Specialty Matched Consultant Advisory Panel review 3/18/2020. No change to policy statements. (krc)

10/27/20 Added the following requirements to "When Covered" section: "Trastuzumab (Hereptin) and trastuzumab biosimilars (trastuzumab-dkst, trastuzumab-pkrb, trastuzumab-dttb, trastuzumab-qyyp, trastuzumab-anns) may be considered medically necessary when the following criteria are met: If the request is for trastuzumab (Herceptin) or non-preferred trastuzumab biosimilars, then both of the following criteria are met: patient has a documented serious adverse event that required medical intervention to <u>both</u> preferred trastuzumab biosimilar products [trastuzumab-anns (Kanjinti), trastuzumab-dkst (Ogivri)] that is not anticipated with the requested product; AND prescriber has completed and submitted an FDA MedWatch Adverse Event Reporting Form." Medical Director review 10/2020. **Policy notification given 10/27/2020 for effective date 1/1/2021**. (krc)