



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Subject **Trastuzumab (Herceptin®)**

Effective Date 3/15/2011
Next Review Date.....3/15/2012
Coverage Position Number..... 5106

Table of Contents

Coverage Policy	1
General Background	2
Coding/Billing Information	5
References	6

Hyperlink to Related Coverage Policies

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

CIGNA covers trastuzumab (Herceptin®) as medically necessary for ANY of the following indications:

- breast cancer that is human epidermal growth factor receptor 2 (HER2)-overexpressing for **EITHER** adjuvant therapy or treatment of metastatic disease
- metastatic gastric or gastroesophageal junction adenocarcinoma that is HER2-overexpressing when there has been no prior treatment for metastatic disease

When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to trastuzumab (Herceptin®).

FDA Approved Indications

Adjuvant Breast Cancer

Herceptin is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk breast cancer as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel with docetaxel and carboplatin as a single agent following multi-modality anthracycline based therapy.

Metastatic Breast Cancer

Herceptin is 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.

Metastatic Gastric Cancer

Herceptin is indicated, 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.

FDA Recommended Dosing

Adjuvant Treatment, Breast Cancer

Administer according to one of the following doses and schedules for a total of 52 weeks of Herceptin therapy: During and following paclitaxel, docetaxel, or docetaxel/carboplatin - Initial dose of 4mg/kg as an intravenous infusion over 90 minutes then at 2 mg/kg as an intravenous infusion over 30 minutes weekly during chemotherapy for the first 12 weeks (paclitaxel or docetaxel) or 18 weeks (docetaxel/carboplatin) or one week following the last weekly dose of Herceptin, administer Herceptin at 6 mg/kg as an intravenous infusion over 30-90 minutes every three weeks. As a single agent within three weeks following completion of multi-modality, anthracycline-based chemotherapy regimens - Initial dose at 8 mg/kg as an intravenous infusion over 90 minutes and subsequent doses at 6 mg/kg as an intravenous infusion over 30-90 minutes every three weeks.

Metastatic Treatment, Breast Cancer

Administer Herceptin, alone or in combination with paclitaxel, at an initial dose of 4 mg/kg as a 90 minute intravenous infusion followed by subsequent once weekly doses of 2 mg/kg as 30 minute intravenous infusions until disease progression.

Black Box Warning

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, and PULMONARY TOXICITY

Cardiomyopathy - Herceptin can result in sub-clinical and clinical cardiac failure manifesting as CHF and decreased LVEF. The incidence and severity of left ventricular cardiac dysfunction was highest in patients who received Herceptin concurrently with anthracycline-containing chemotherapy regimens. Evaluate left ventricular function in all patients prior to and during treatment with Herceptin. Discontinue Herceptin treatment in patients receiving adjuvant therapy and strongly consider discontinuation of Herceptin treatment in patients with metastatic breast cancer for clinically significant decrease in left ventricular function. **Infusion Reactions; Pulmonary Toxicity** - Herceptin administration can result in serious infusion reactions and pulmonary toxicity. Fatal infusion reactions have been reported. In most cases, symptoms occurred during or within 24 hours of administration of Herceptin. Herceptin infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinue Herceptin for infusion reactions manifesting as anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome.

Drug Availability

Herceptin is supplied in a multi-use vial containing 440 mg trastuzumab as a lyophilized sterile powder, under vacuum. Each carton contains one vial Herceptin and one vial (20 mL) of Bacteriostatic Water for Injection (BWF1), USP, containing 1.1% benzyl alcohol as a preservative.

General Background

Pharmacology

Trastuzumab is a recombinant deoxyribonucleic acid (DNA)-derived humanized monoclonal antibody that selectively binds the extracellular domain of the human epidermal growth factor receptor 2 (HER2) protein. The HER2 proto-oncogene encodes a transmembrane receptor protein. HER2 protein overexpression is observed in 20–30% of primary breast cancers and also in ovarian, lung, stomach and colorectal cancers. HER2/neu overexpression has been linked to a poor prognosis. Trastuzumab inhibits the proliferation of human tumor cells that overexpress HER2. It is a mediator of antibody-dependent cellular cytotoxicity. Trastuzumab-mediated

antibody-dependent cellular cytotoxicity is preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

Guidelines

The National Comprehensive Cancer Network (NCCN) recommends trastuzumab as follows:

Breast Cancer

Grade 1

Preoperative chemotherapy in combination with paclitaxel followed by FEC/CEF (fluorouracil, epirubicin, and cyclophosphamide) regimen with trastuzumab for patients with human epidermal growth factor receptor 2 (HER2)-positive stage IIA, IIB, or T3, N1, M0 disease who desire breast preservation and fulfill criteria for breast-conserving surgery except for tumor size or for patients with locally advanced disease (stage IIIA, IIIB, or IIIC)

Adjuvant chemotherapy for human epidermal growth factor receptor 2 (HER2)-positive, stage I, IIA, IIB, or T3, N1, M0 disease (ductal, lobular, mixed, or metaplastic histologies) that is node-positive, node-negative with tumor 0.5 cm or greater in hormone receptor-negative patients, or node-negative with tumor 0.6 to 1 cm, grade 2 or 3, or with unfavorable features or tumor greater than 1 cm in hormone receptor-positive patients, or for patients with locally advanced disease (stages IIIA, IIIB, or IIIC) concurrently with paclitaxel following AC (doxorubicin and cyclophosphamide) regimen as preferred regimen; in TCH (docetaxel, carboplatin, and trastuzumab) regimen as preferred regimen; in combination with docetaxel followed by FEC/CEF (fluorouracil, epirubicin, and cyclophosphamide) regimen; following chemotherapy; in combination with docetaxel following AC regimen.

Grade 2A

Used in combination with aromatase inhibition for the treatment of recurrent or stage IV estrogen receptor-positive, human epidermal growth factor receptor 2 (HER2)-positive disease in postmenopausal women* who have received no prior endocrine therapy within one year. 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.

Preferred regimen for patients with human epidermal growth factor receptor 2 (HER2)-positive recurrent or metastatic breast cancer that is hormone receptor-negative or hormone receptor-positive and endocrine refractory and not characterized by bone or soft tissue involvement only or asymptomatic visceral disease as first-line chemotherapy in combination with docetaxel, vinorelbine, or capecitabine or with paclitaxel with or without carboplatin or treatment for trastuzumab-exposed HER2-positive disease in combination with lapatinib without cytotoxic therapy, with docetaxel, vinorelbine, or capecitabine, or with paclitaxel with or without carboplatin.

Esophageal Cancer

Grade 2A

Used in combination with systemic chemotherapy for the treatment of patients with advanced gastroesophageal junction adenocarcinoma that is HER-2-positive by a standardized method.

Gastric Cancer

Grade 2A

Used in combination with systemic chemotherapy for the treatment of patients with advanced gastric cancer that is HER-2 positive as determined by a standardized method.

Clinical Efficacy

Trastuzumab pharmacokinetics was evaluated in patients with metastatic breast cancer. Short duration intravenous (IV) infusions of 10–500 mg once weekly demonstrated dose-dependent pharmacokinetics. The mean half-life increased, and clearance decreased with increasing doses. The half-life averaged 1.7 days at the 10 mg dose level and 12 days at the 500 mg dose level. The volume of distribution approximates that of serum volume (44 mL/kg). A mean half-life of 5.8 days was observed in studies evaluating a trastuzumab 4 mg/kg loading dose followed by a weekly maintenance dose of 2 mg/kg. Steady-state concentrations were achieved between weeks 16 and 32 of therapy.

In the clinical studies, patient eligibility was determined by testing tumor specimens for overexpression of HER2 protein. Specimens were tested with a research-use-only immunohistochemical (IHC) assay (referred to as the Clinical Trial Assay, CTA) and scored as 0, 1+, 2+, or 3+, with 3+ indicating the strongest positivity. Only patients with 2+ or 3+ positive tumors were eligible. Data from the efficacy trials suggest that the beneficial treatment effects were largely limited to patients with the highest level of HER2 protein overexpression (3+).

The safety and efficacy of trastuzumab were studied in combination with chemotherapy in a randomized, controlled clinical trial in combination enrolling 469 patients and as a single agent in an open-label clinical trial enrolling 222 patients. Both trials studied patients with metastatic breast cancer whose tumors overexpress the HER2 protein with 2+ or 3+ levels of overexpression (based on a 0–3+ scale). A multi-center, randomized, controlled clinical trial was conducted in 469 patients with metastatic breast cancer who had not been previously treated with chemotherapy for metastatic disease. Patients were randomized to receive chemotherapy alone or in combination with trastuzumab given intravenously as a 4 mg/kg loading dose followed by weekly doses of trastuzumab at 2 mg/kg. For those who had received prior anthracycline therapy in the adjuvant setting, chemotherapy consisted of paclitaxel (175 mg/m² over three hours every 21 days for at least six cycles); for all other patients, chemotherapy consisted of anthracycline plus cyclophosphamide (AC: doxorubicin 60 mg/m² or epirubicin 75 mg/m² plus 600 mg/m² cyclophosphamide every 21 days for six cycles). Patients treated with the combination of trastuzumab plus chemotherapy experienced a longer time to disease progression, a higher overall response rate, a longer median duration of response and a higher one-year survival rate. Similar results were observed in patients treated with trastuzumab and either paclitaxel or anthracycline, although the addition of trastuzumab appeared to enhance the efficacy of paclitaxel more than the other regimen. The degree of HER2 overexpression was a predictor of response. The overall incidence of adverse effects was not increased by the addition of trastuzumab to therapy; however, cardiac dysfunction occurred much more frequently in patients treated with trastuzumab plus the anthracycline regimen compared to patients treated with the anthracycline regimen alone, paclitaxel alone or paclitaxel plus trastuzumab.

Two Phase III, randomized, multi-center, controlled trials, sponsored by the National Cancer Institute-sponsored Cooperative Groups, studied four cycles of doxorubicin (adriamycin) and cyclophosphamide followed by paclitaxel, either every three weeks or weekly for 12 weeks, compared with the same regimen plus 52 weeks of trastuzumab beginning with the first dose of paclitaxel. The results showed that women who received trastuzumab combined with chemotherapy had fewer relapses for up to three years after surgery. The estimated three-year disease-free rates were 87% in women receiving trastuzumab and chemotherapy and 75% in those receiving chemotherapy alone.

The National Surgical Adjuvant Breast and Bowel Project trial B-31 in 2043 patients enrolled compared two regimens:

- doxorubicin and cyclophosphamide followed by paclitaxel every three weeks (group 1) – This was considered the controlled group
- same regimen as above plus 52 weeks of trastuzumab beginning with the first dose of paclitaxel (group 2)

The North Central Cancer Treatment Group trial N9831 in 1633 patient enrolled compared three regimens:

- doxorubicin and cyclophosphamide followed by weekly paclitaxel (group A) - this was considered the controlled group
- same regimen as above followed by 52 weeks of trastuzumab after paclitaxel (group B) – However this group was excluded because trastuzumab was not given concurrently with paclitaxel.
- same regimen plus 52 weeks of trastuzumab initiated concomitantly with paclitaxel (group C)

The primary end point of these studies was disease-free survival. The median follow-up was 2.0 years (2.4 years in trial B-31 and 1.5 years in trial N9831). There were a total of 394 events, including recurrent, second primary cancer, or death before recurrence occurred (261 events in the control group and 133 events in the trastuzumab combination group). The hazard ratio for a first event in the trastuzumab group, as compared with the control group, was 0.48. The percentages of patients alive and disease-free at three years were 75% in the control group and 87% in the trastuzumab group. At four years, the respective percentages were 67% and 85% ($p < 0.0001$). This difference crossed the early stopping boundary. After three years, the absolute survival rate at three years was 94% in the trastuzumab group and 92% in the control group and at four years, the respective rates were 87% and 91%. ($p = 0.015$). Distant metastases were reported in 193 patients in the control group and 96 in the trastuzumab group. The hazard ratio for a first distant recurrence was 0.47 in the trastuzumab group as

compared with the control group ($p < 0.0001$). At three years, 90% of women in the trastuzumab group were free of distant recurrence, as compared with 82% of women in the control group. At four years, the results were 90% and 74%, respectively.

About 22% of patients with advanced gastric cancer were found to have tumors that overexpress human epidermal growth-factor receptor 2 (HER2), and these patients had significantly improved overall survival when trastuzumab was added to chemotherapy, compared with chemotherapy alone. The results come from the ToGA study, which was conducted in 594 patients with HER2-positive disease, who were identified after nearly 4000 patients with advanced gastric cancer were screened. All of the patients received chemotherapy (most commonly cisplatin and capecitabine), but sometimes cisplatin and 5-fluorouracil and half were randomized to also receive trastuzumab (6 mg/kg every 3 weeks until progression). The trial was stopped early (after a median follow-up of 17 months) because of the benefit seen. The improvement in overall survival was 2.7 months, from 11.1 months in the chemotherapy group to 13.8 months in the trastuzumab.

In addition to the impact on survival, trastuzumab improved all of the secondary end points, he noted, including progression-free survival (increased from 5.2 months to 6.7 months) and overall response rate (increased from 34.5% to 47%, which is "statistically significant and clinically meaningful." The addition of trastuzumab did not affect safety, the overall rate of grade 3/4 adverse events was similar in both groups. There were 3 treatment-related deaths in the trastuzumab group and 1 in the chemotherapy group. In particular, there was no concern over cardiac toxicity, he added. The incidence of cardiac failure was very rare (<1% in both groups), although asymptomatic decreases in left ventricular ejection fraction were more frequent in the trastuzumab group than in the chemotherapy group (4%–5% vs 1%).

Ongoing Studies

Currently there is an active Phase II study being conducted for the use of Herceptin in advanced urothelial cancer. A phase II study has been completed for combination paclitaxel, carboplatin, and trastuzumab. Toxicity appears no worse than cytotoxic therapy alone. Overall survival is similar to historical data using carboplatin and paclitaxel alone. However, patients with 3+ HER-2/*neu* expression did well in contrast to historical data suggesting potential benefit for trastuzumab in this rare subset of NSCLC. Critical assessment of trastuzumab's role in advanced NSCLC will require phase III trials.

Adverse Reactions

Trastuzumab administration can result in severe hypersensitivity reactions (including anaphylaxis), infusion reactions, and pulmonary events. Rarely, these have been fatal. In most cases, symptoms occurred during or within 24 hours of administration of trastuzumab. The infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinuation of therapy should be strongly considered for patients who develop anaphylaxis, angioedema, or acute respiratory distress syndrome.

The most common adverse reactions in patients receiving Herceptin are fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

HCPCS Codes	Description
J9355	Injection, trastuzumab, 10 mg

ICD-9-CM Diagnosis Codes	Description
--------------------------	-------------

151.0-151.9	Malignant neoplasm of stomach
174.0-174.9	Malignant neoplasm of female breast
175.0-175.9	Malignant neoplasm of male breast

References

1. Chustecka, Zosia. American Society of Clinical Oncology (ASCO) 2009: Herceptin in Gastric Cancer — Practice Changing Data. ASCO 45th Meeting.
2. ClinicalTrials.gov. Trastuzumab (Herceptin), Paclitaxel, Carboplatin and Gemcitabine in Advanced Urothelial Cancer. Available at <http://clinicaltrials.gov/ct2/show/NCT00151034?term=herceptin&rank=15>
3. Food and Drug Administration - FDA News: FDA Expands Use of Herceptin for Early Stage Breast Cancer After Primary Therapy. November 16, 2006. Available at: <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01511.html>. Accessed on November 22, 2006.
4. Genetech. Herceptin (trastuzumab) package insert. South San Francisco, CA: Genentech, Inc. March 2009.
5. Langer, C. et. al. Trastuzumab in the Treatment of Advanced Non-Small-Cell Lung Cancer: Is There a Role? Focus on Eastern Cooperative Oncology Group Study 2598. Journal of Clinical Oncology, Vol 22, No 7 (April 1), 2004: pp. 1180-1187.
6. McEvoy GK, ed. AHFS 2010 Drug Information. Bethesda, MD: American Society of Health-Systems Pharmacists, Inc; 2010.
7. NCCN Drugs & Biologics Compendium™. Herceptin® (trastuzumab) Copyright 2010, National Comprehensive Cancer Network (NCCN).
8. Romond E, Perez EA, Bryant J, et al. Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer. NEJM. 2006.16;353:1673-1684.
9. Romond E, Perez EA, Bryant J, et al. Doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab as adjuvant therapy for patients with HER-2 positive operable breast cancer; combined analysis of NSABP-B31/NCCTG-N9831. Presented at the 41st Annual Meeting of the American Society of Clinical Oncology in Orlando, Florida; May 13-17; 2005.

“CIGNA”, “CIGNA HealthCare” and the “Tree of Life” logo are registered service marks of CIGNA Intellectual Property, Inc., licensed for use by CIGNA Corporation and its operating subsidiaries. All products and services are provided by such operating subsidiaries and not by CIGNA Corporation. Such operating subsidiaries include Connecticut General Life Insurance Company, CIGNA Health and Life Insurance Company, CIGNA Behavioral Health, Inc., CIGNA Health Management, Inc., and HMO or service company subsidiaries of CIGNA Health Corporation and CIGNA Dental Health, Inc. In Arizona, HMO plans are offered by CIGNA HealthCare of Arizona, Inc. In California, HMO plans are offered by CIGNA HealthCare of California, Inc. In Connecticut, HMO plans are offered by CIGNA HealthCare of Connecticut, Inc. In North Carolina, HMO plans are offered by CIGNA HealthCare of North Carolina, Inc. In Virginia, HMO plans are offered by CIGNA HealthCare Mid-Atlantic, Inc. All other medical plans in these states are insured or administered by Connecticut General Life Insurance Company or CIGNA Health and Life Insurance Company.