**Herceptin**

Effective Date: 10/22/13  
Date Developed: 9/3/13 by Albert Reeves MD  
Last Approval Date: 1/26/16, 1/24/17, 1/23/18, 1/22/19

**Pharmacologic Category:** AntineoplasticAgent, Anti-HER2, Antineoplastic Agent, Monoclonal Antibody

**Pre-authorization Criteria:** Treatment (adjuvant) of HER2 overexpressing breast cancer as part of a combination regimen with doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel; in combination with docetaxel and carboplatin; as a single agent following anthracycline-based combination treatment; treatment of HER2 metastatic breast cancer in combination with paclitaxel as first-line treatment or as a single agent in patients who have received prior chemotherapy regimens for treatment of metastatic disease; treatment of HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma in combination with cisplatin and either capecitabine or fluorouracil in patients who have not received prior treatment for metastatic disease.

**Dosing: Adult**

**Note:** Do NOT substitute conventional trastuzumab for or with ado-trastuzumab emtansine; products are different and are NOT interchangeable. Details concerning dosing in combination regimens should also be consulted.

**Breast cancer, adjuvant treatment, HER2+:** I.V. infusion:

**With concurrent paclitaxel or docetaxel:**

Initial loading dose: 4 mg/kg infused over 90 minutes, followed by

Maintenance dose: 2 mg/kg infused over 30 minutes weekly for total of 12 weeks, followed 1 week later (when concurrent chemotherapy completed) by 6 mg/kg infused over 30-90 minutes every 3 weeks for total therapy duration of 52 weeks

**With concurrent docetaxel/carboplatin:**

Initial loading dose: 4 mg/kg infused over 90 minutes, followed by
Maintenance dose: 2 mg/kg infused over 30 minutes weekly for total of 18 weeks, followed 1 week later (when concurrent chemotherapy completed) by 6 mg/kg infused over 30-90 minutes every 3 weeks for total therapy duration of 52 weeks

Following completion of anthracycline-based chemotherapy:

Initial loading dose: 8 mg/kg infused over 90 minutes, followed by

Maintenance dose: 6 mg/kg infused over 30-90 minutes every 3 weeks for total therapy duration of 52 weeks

Breast cancer, metastatic, HER2+ (either as a single agent or in combination with paclitaxel):

I.V. infusion:

Initial loading dose: 4 mg/kg infused over 90 minutes, followed by

Maintenance dose: 2 mg/kg infused over 30 minutes weekly until disease progression

Gastric cancer, metastatic, HER2+ (in combination with cisplatin and either capecitabine or fluorouracil for 6 cycles followed by trastuzumab monotherapy; Bang, 2010; Van Cutsem, 2009): I.V. infusion:

Initial loading dose: 8 mg/kg infused over 90 minutes, followed by

Maintenance dose: 6 mg/kg infused over 30-90 minutes every 3 weeks until disease progression

Missed doses (Canadian labeling, 2012): If a dose is missed by ≤1 week, the usual maintenance dose (based on patient’s schedule) should be administered as soon as possible (do not wait until the next planned cycle); if a dose is missed by >1 week, then a loading dose (4 mg/kg if patient receives trastuzumab weekly; 8 mg/kg if on an every-3-week schedule) should be administered, followed by the usual maintenance dose and schedule.

Breast cancer, metastatic, HER2+ (unlabeled combinations):

Trastuzumab, pertuzumab, and docetaxel (in patients with no prior anti-HER2 therapy or chemotherapy to treat metastatic disease): Initial: 8 mg/kg followed by a maintenance dose of 6 mg/kg every 3 weeks until disease progression or unacceptable toxicity (Baselga, 2012)
Trastuzumab and lapatinib (in patients with progression on prior trastuzumab containing therapy): Initial: 4 mg/kg followed by a maintenance dose of 2 mg/kg every week (Blackwell, 2010; Blackwell, 2012)

Administration

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Check label to ensure appropriate product is being administered (conventional trastuzumab and ado-trastuzumab are different products and are NOT interchangeable).

Administered by I.V. infusion; loading doses are infused over 90 minutes; maintenance doses may be infused over 30 minutes if tolerated. Do not administer with D5W. Do not administer I.V. push or by rapid bolus.

Observe patients closely during the infusion for fever, chills, or other infusion-related symptoms. Treatment with acetaminophen, diphenhydramine, and/or meperidine is usually effective for managing infusion-related events.

Hazardous agent; use appropriate precautions for handling and disposal (meets NIOSH, 2012 criteria).

Adverse Reactions:

>10%:

Cardiovascular: LVEF decreased (4% to 22%)

Central nervous system: Pain (47%), fever (6% to 36%), chills (5% to 32%), headache (10% to 26%), insomnia (14%), dizziness (4% to 13%)

Dermatologic: Rash (4% to 18%)
Gastrointestinal: Nausea (6% to 33%), diarrhea (7% to 25%), vomiting (4% to 23%), abdominal pain (2% to 22%), anorexia (14%)

Neuromuscular & skeletal: Weakness (4% to 42%), back pain (5% to 22%)

Respiratory: Cough (5% to 26%), dyspnea (3% to 22%), rhinitis (2% to 14%), pharyngitis (12%)

Miscellaneous: Infusion reaction (21% to 40%, chills and fever most common; severe: 1%), infection (20%)

1% to 10%:

Cardiovascular: Peripheral edema (5% to 10%), edema (8%), HF (2% to 7%; severe: <1%), tachycardia (5%), hypertension (4%), arrhythmia (3%), palpitation (3%)

Central nervous system: Depression (6%)

Dermatologic: Acne (2%), nail disorder (2%), pruritus (2%)

Gastrointestinal: Constipation (2%), dyspepsia (2%)

Genitourinary: Urinary tract infection (3% to 5%)

Hematologic: Anemia (4%), leukopenia (3%)

Neuromuscular & skeletal: Paresthesia (2% to 9%), bone pain (3% to 7%), arthralgia (6% to 8%), myalgia (4%), muscle spasm (3%), peripheral neuritis (2%), neuropathy (1%)

Respiratory: Sinusitis (2% to 9%), nasopharyngitis (8%), upper respiratory infection (3%), epistaxis (2%), pharyngolaryngeal pain (2%)

Miscellaneous: Flu-like syndrome (2% to 10%), accidental injury (6%), influenza (4%), allergic reaction (3%), herpes simplex (2%)

Warnings;
Cardiomyopathy: [U.S. Boxed Warning]: Trastuzumab is associated with symptomatic and asymptomatic reductions in left ventricular ejection fraction (LVEF) and heart failure (HF); the incidence is highest in patients receiving trastuzumab with an anthracycline-containing chemotherapy regimen. Evaluate LVEF in all patients prior to and during treatment; discontinue for cardiomyopathy. Extreme caution should be used in patients with pre-existing cardiac disease or dysfunction. Prior or concurrent exposure to anthracyclines or radiation therapy significantly increases the risk of cardiomyopathy; other potential risk factors include advanced age, high or low body mass index, smoking, diabetes, hypertension, and hyper-/hypothyroidism. Discontinuation should be strongly considered in patients who develop a clinically significant reduction in LVEF during therapy; treatment with HF medications (eg, ACE inhibitors, beta-blockers) should be initiated. Withhold treatment for ≥16% decrease from pretreatment levels or LVEF below normal limits and ≥10% decrease from baseline (see Dosage Adjustment for Cardiotoxicity). Cardiomyopathy due to trastuzumab is generally reversible over a period of 1-3 months after discontinuation. Trastuzumab is also associated with arrhythmias, hypertension, mural thrombus formation, stroke, and even cardiac death.

- Infusion reactions: [U.S. Boxed Warning]: Infusion reactions (including fatalities) have been associated with use; discontinue for anaphylaxis or angioedema. Most reactions occur during or within 24 hours of the first infusion; interrupt infusion for dyspnea or significant hypotension; monitor until symptoms resolve. Infusion reactions may consist of fever and chills, and may also include nausea, vomiting, pain, headache dizziness, dyspnea, hypotension, rash and weakness. Retreatment of patients who experienced severe hypersensitivity reactions has been attempted (with premedication). Some patients tolerated retreatment, while others experienced a second severe reaction.

- Pulmonary toxicity: [U.S. Boxed Warning]: May cause serious pulmonary toxicity (dyspnea, hypoxia, interstitial pneumonitis, pulmonary infiltrates, pleural effusion, noncardiogenic pulmonary edema, pulmonary insufficiency, acute respiratory distress syndrome [ARDS], and/or pulmonary fibrosis); discontinue
for ARDS or interstitial pneumonitis. Use caution in patients with pre-existing pulmonary disease or patients with extensive pulmonary tumor involvement; these patient populations may have more severe toxicity. Pulmonary events may occur during or within 24 hours of administration; delayed reactions have occurred.

- Renal toxicity: Rare cases of nephrotic syndrome with evidence of glomerulopathy have been reported, with an onset of 4-18 months from trastuzumab initiation; complications may include volume overload and HF. The incidence of renal impairment was increased in metastatic gastric cancer patients when trastuzumab is added to chemotherapy

Monitoring Parameters:

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Assessment for HER2 overexpression and HER2 gene amplification by validated immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH) methodology (pretherapy); test should be specific for cancer type (breast vs gastric cancer). Pregnancy test (prior to treatment). Monitor vital signs during infusion; signs and symptoms of cardiac dysfunction; LVEF (baseline, every 3 months during treatment, upon therapy completion and if component of adjuvant therapy, every 6 months for at least 2 years; if treatment is withheld for significant LVEF dysfunction, monitor LVEF at 4-week intervals); signs and symptoms of infusion reaction; if pregnancy inadvertently occurs during treatment,

References:


**Revision History:**

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Date Approved by P&T Committee: 1/28/14
Date Reviewed/No Updates: 1/13/15 by C. Sanders, MD
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Date Approved by P&T Committee: 1/23/18
Date Reviewed/No Updates: 1/22/19 by C. Sanders, MD; R. Sterling, MD
Date Approved by P&T Committee: 1/22/19

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<th>Content Revised (Yes/No)</th>
<th>Contributors</th>
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