

Trastuzumab (Herceptin®)**Criteria for Use****March 2015**

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or <http://vaww.pbm.va.gov> for further information.

Exclusion Criteria If the answer to ANY item below is met, then the patient should NOT receive trastuzumab.

- Tumor tissue does NOT overexpress HER2 protein (HER2 positive status defined as IHC 3+ or FISH amplification ratio ≥ 2.0)
- Unwilling to transfer oncology care to VA provider
- History of non-compliance with follow-up appointments or laboratory visits
- Known hypersensitivity to trastuzumab or any of its excipients (L-histidine acetate, sucrose, polysorbate 20)
- Clinically significant cardiovascular disease defined as:
 - Baseline Left Ventricular Ejection Fraction (LVEF) $< 55\%$ via MUGA or echocardiography ($<50\%$ if metastatic disease)
 - Uncontrolled hypertension or arrhythmia
 - Myocardial infarction within prior 6 months
 - CHF (NYHA Class 3 or 4)
 - Cumulative prior anthracycline exposure $> 360 \text{ mg/m}^2$ of doxorubicin or its equivalent
- Pregnancy

Inclusion Criteria Trastuzumab may be used in any one of the following settings:

- Neoadjuvant/Adjuvant Breast Cancer Setting.** Diagnosis of breast cancer with node-positive disease or node-negative with high-risk features (i.e. tumor size) and a candidate for neoadjuvant/adjuvant therapy; trastuzumab should be given for a total of 52 weeks.
- Metastatic Breast Cancer (MBC) Setting.** Diagnosis of MBC. Trastuzumab may be used as **first-line therapy** either with pertuzumab and a taxane (docetaxel or paclitaxel), **OR** with active cytotoxic agents in MBC (i.e. paclitaxel, docetaxel, vinorelbine, capecitabine, carboplatin)
 - Goals of care and role of Palliative Care consult have been discussed and documented.
- Metastatic Breast Cancer Setting.** As **subsequent therapy** either alone or in combination with active cytotoxic agents in MBC (i.e. paclitaxel, docetaxel, vinorelbine, capecitabine, carboplatin). See Issues for Consideration.
 - Goals of care and role of Palliative Care consult have been discussed and documented.
- Metastatic Gastric/Gastroesophageal Junction Adenocarcinoma Setting.** As a component of first-line therapy in combination with cisplatin and 5-fluorouracil or capecitabine. See Issues for Consideration.
 - Goals of care and role of Palliative Care consult have been discussed and documented.

AND the following:

- Eastern Cooperative Oncology Group (ECOG) Performance Status 0-2[†]

For women of childbearing potential

- Pregnancy must be excluded prior to receiving trastuzumab and patient provided contraceptive counseling on potential risk vs. benefit of taking trastuzumab if patient were to become pregnant

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Updated versions may be found at <http://www.pbm.va.gov> or <https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx>

Dosage and Administration (refer to prescribing information for administration details and dose modifications)

- Do **NOT** substitute **trastuzumab** for **ado-trastuzumab emtansine!**
- Refer to PI for dose modification guidelines for the following:
 - Infusion reactions
 - Cardiomyopathy
- Use of intrathecal trastuzumab (off-label) will require drug reconstitution with preservative-free diluent, NOT the diluent included from the manufacturer in packaging, which contains 1.1% benzyl alcohol.

Monitoring

- LVEF at baseline and every 3 months during and upon completion of trastuzumab
- Repeat LVEF measurement at 4-week intervals if drug is withheld for significant LV dysfunction
- LVEF measurements every 6 months for at least 2 years following completion of trastuzumab as adjuvant therapy
- Trastuzumab should be withheld in situations where there is $\geq 16\%$ absolute decrease in LVEF from baseline values or an LVEF value that is below institutional limits of normal and $\geq 10\%$ absolute decrease from baseline values.
- Observe patients closely for possible hypersensitivity reactions. Onset and clinical course of reactions are variable. Interrupt trastuzumab if patient experiences dyspnea and significant hypotension. Consider permanent discontinuation in patients with severe reactions. Premedication can be considered, yet recognize that recurrent reactions are possible despite premedication.
- Severity and duration of diarrhea
- Fever and signs/symptoms of infection
- CBC with differential at baseline and each month. Trastuzumab can potentiate the risk of chemotherapy-induced neutropenia when given with myelosuppressive chemotherapy. Anticipation of Grade 3, 4 neutropenia and possibly febrile neutropenia should be a consideration prior to initiating therapy.
- Pregnancy test prior to initiation of therapy (if child-bearing potential) and as clinically indicated. Boxed warning: Exposure to trastuzumab during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death.

Issues for Consideration

- **Subsequent Therapy.** There is no prospective data to guide the duration of HER2-directed therapy in MBC. Use of HER2-directed therapy beyond the second-line setting in MBC has been shown to provide a benefit in PFS (TH3RESA); improvement in OS has not been demonstrated. Patients should be aware of risks (toxicity, inconvenience, cost) vs. benefits (improved PFS) when considering ongoing HER2-directed therapy.
- **Gastric/ Gastroesophageal Junction (GEJ) Setting.** FDA-approval is based upon clinical evidence of an OS benefit in combination with cisplatin and a fluoropyrimidine (capecitabine or fluorouracil) in patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease. Use of trastuzumab in combination with other regimens is supported by preliminary evidence from an observational study that suggests a PFS-benefit similar to that noted in the ToGA trial. An OS benefit with these other regimens has not been demonstrated.

Discontinuation Criteria

- Evidence of disease progression in the form of radiographic progression, clinical deterioration and serum tumor markers (i.e. CA 15-3, CA 27.29, CEA, circulating tumor cells)

† http://www.ecog.org/general/perf_stat.html