Drug Monograph

A - Drug Name

trastuzumab

COMMON TRADE NAME(S): Herceptin®; Kanjinti™; Ogivri™; Trazimera™; Herzuma®; Ontruzant®

- Different trastuzumab products are **not interchangeable**.
- For additional information on biosimilars, refer to:
  - Position Statements for the Clinical Operational Implementation of Oncology Biosimilars from the pan-Canadian Clinical Operations Working Group
  - Clinician Fact Sheet

back to top

B - Mechanism of Action and Pharmacokinetics

Trastuzumab is a recombinant DNA-derived humanized monoclonal antibody that selectively targets the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2). Trastuzumab inhibits the proliferation of tumour cells that overexpress HER2 and mediates antibody dependent cell mediated cytotoxicity (ADCC) on HER2 overexpressing cells.

Absorption	Not orally bioavailable. Steady state levels reached approximately 20 weeks (weekly breast dosing) and 52 weeks (q3w breast dosing).	
Distribution	Trastuzumab follows a non-linear but dose dependent pharmacokinetic profile. Clearance decreases and $T_{1/2}$ increases with increasing dose. Patients with high circulating levels of the external domain of HER2 may have lower trastuzumab levels or take longer to achieve steady state levels.	
	Cross blood brain barrier?	Minimal
	PPB	No information found

Metabolism	Likely clearance of IgG through the reticuloendothelial system.	
	Active metabolites	no
	Inactive metabolites	no
Elimination	Higher clearance observed in metastatic gastric cancer patients, leading to lower exposure at steady state than metastatic breast cancer patients.	
	Urine	no
	Half-life	28.5 days (weekly breast regimen); 12.2 days (q3w gastric regimen); may persist in circulation for approximately 24 weeks (range 22-28 weeks).

back to top

C - Indications and Status

Health Canada Approvals:

- Breast cancer
- Adenocarcinoma of the stomach or gastro-esophageal junction

Refer to the product monograph for a full list and details of approved indications.

back to top

D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: None

The following table contains adverse effects mainly reported after 1 year of adjuvant trastuzumab monotherapy (sequential), where the incidence is greater (≥1%) than the observation arm. Adverse events from other studies or post-marketing may also be included. Side effects marked with an asterisk indicate incidences reported from breast cancer clinical trials in combination with chemotherapy.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (<1%) *	E
	Arterial thromboembolism (rare)*	D
	Cardiotoxicity (6%)	D
	Hypertension (6%)	E
	Palpitations (4%)	E
	Venous thromboembolism (3%) (severe)*	E
Dermatological	Nail disorder (3%)	E
	Rash, pruritus (6%)	E
Gastrointestinal	Abdominal pain (4%)	E
	Constipation (3%)	E
	Diarrhea (9%)	E
	Mucositis (2%)	E
	Nausea, vomiting (8%)	I
	Weight changes (2%)	E
General	Edema (7%)	E
	Fatigue (12%)	E
	Flu-like symptoms (7%)	I
	Pain (4%)	E
Hematological	Myelosuppression, bleeding (4%) (grade 3/4) (combined with chemotherapy; infrequent as a single agent)	E
Hepatobiliary	↑ LFTs (rare)*	D
	Pancreatitis (rare)*	E
Hypersensitivity	Hypersensitivity (<1%)	I
Infection	Infection (6%)	E

Musculoskeletal	Musculoskeletal pain (13%)	D
Neoplastic	Secondary malignancy (1%) *	D
Nervous System	Anxiety (3%)	E
	Depression (5%)	E D
	Dizziness (5%)	E
	Headache (12%)	E
	Paresthesia (2%)	E
	Sleep disorder (6%)	E
	Vertigo (2%)	E
Renal	Renal failure (rare)*	E D
Respiratory	Cough, dyspnea (7%)	E
	Interstitial lung disease (rare)	E
	Other - Lung fibrosis (rare)	D
Vascular	Hot flashes (10%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for trastuzumab include musculoskeletal pain, fatigue, headache, hot flashes, diarrhea, nausea, vomiting, cough, dyspnea, edema, flu-like symptoms and cardiotoxicity.

Serious adverse effects associated with trastuzumab include **infusion-related reactions** (with acute respiratory distress syndrome) and **cardiotoxicity**. When given in combination with chemotherapy, the incidence of most adverse effects increases over those expected for either agent alone.

Cardiotoxicity (CHF and ventricular dysfunction) of any grade occurs in 4% of metastatic and 5% of adjuvant breast patients predominantly during treatment. The incidence is increased dramatically in combination therapy with an anthracycline. The risk of cardiac dysfunction associated with trastuzumab therapy may be increased in older patients, patients with high BMI, patients with low LVEF, prior or concurrent use of anti-hypertensive medications, patients with pre-existing cardiac disease and patients who have had prior cardiotoxic therapy (e.g. anthracycline therapy or radiation therapy to the chest area). A higher incidence of cardiac events was observed when trastuzumab was given after anthracycline-containing chemotherapy than with non-anthracycline regimens and also when trastuzumab was given concurrently with a taxane than when administered sequentially to a taxane. Rates with non-anthracycline containing regimens such as CRBPDOCETRAS appear to be lower. Cardiotoxicity associated with trastuzumab typically responds to appropriate medical therapy (diuretic, beta-blockers, ACE inhibitors or digoxin, etc.) but may be severe and lead to

cardiac failure with mural thrombi and stroke.

Infusion-associated symptoms are common with trastuzumab. During the first infusion with trastuzumab, chills and/or fever (up to 40%) have been observed. The symptoms are usually mild to moderate in severity and occur infrequently with subsequent trastuzumab infusions. Symptom onset generally occurred during or immediately after the infusion. Delayed reactions have also occurred very rarely; fatalities have occurred within hours and up to one week after the infusion. Interruption of trastuzumab infusion was infrequent.

Severe, including fatal **hypersensitivity reactions** usually occur during or immediately after the infusion, but the onset may be delayed. Reactions were most commonly reported in association with the initial infusion. Rarely symptoms may initially improve and then worsen up to one week after the infusion. Dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, respiratory distress and allergic-like reactions have been described, which can be serious and potentially life-threatening. The trastuzumab infusion should be discontinued in all patients with severe hypersensitivity reactions and carefully monitor these patients until resolution of symptoms. Patients who are experiencing dyspnea at rest (due to pulmonary metastases) may be at increased risk of a fatal infusion reaction – these patients should be treated with extreme caution and risk versus benefit be considered.

Pulmonary events, which may be life-threatening, have been reported to occur from within 24 hours to over 30 days after treatment initiation. Dyspnea, pulmonary infiltrates, pneumonitis, pleural effusions, non-cardiogenic pulmonary edema, and ARDS may occur. Patients with dyspnea at rest (due to intrinsic lung disease or tumour involvement with the lungs) and patients who have had prior radiation or chemotherapy may be at greater risk of pulmonary toxicity. Pneumonitis and pulmonary fibrosis have also been described. In early and metastatic breast cancer clinical trials, the incidence of pulmonary toxicities was increased in patients treated with chemotherapy and trastuzumab versus chemotherapy alone.

Although **gastrointestinal effects** (e.g. diarrhea) are generally mild to moderate and **hematologic** effects occur infrequently, increased incidences of these effects are observed in patients receiving combination therapy with trastuzumab and cytotoxic chemotherapy.

back to top

E - Dosing

Do not administer as an IV push or bolus.

NOTE: Different trastuzumab products are **non-interchangeable**. There have been fatal reports where the incorrect trastuzumab product was administered to patients with breast cancer in the clinical trials setting.

Adults:

*3 weekly -
loading dose: 8mg/kg administered as a 90-minute infusion.
maintenance dose: 6mg/kg administered as a 30-minute infusion† every 3 weeks.

**Weekly -
loading dose: 4mg/kg administered as a 90-minute infusion.
maintenance dose: 2mg/kg administered as a 30-minute infusion† weekly.

* Health Canada approved dosing for early breast cancer and gastric cancer; dosing has been used in clinical trials for metastatic breast cancer.
** Health Canada approved dosing for metastatic and early breast cancer.
†Infuse maintenance dose over 30 minutes if the loading dose is well-tolerated.

Dosage with Toxicity:

Dosage with Myelosuppression: No adjustment required.

Dosage with Cardiotoxicity:

Product Monograph Recommendations

- Trastuzumab should be held with a fall in LVEF (if LVEF falls ≥10 points from baseline and/or if LVEF falls to < 50%). Repeat LVEF in 3 weeks and consider discontinuing. Discontinue if clinically significant cardiac dysfunction or cardiac failure develops.

Canadian Consensus Guidelines: Discontinue if symptomatic.

Management of trastuzumab therapy in adjuvant breast cancer patients with asymptomatic decreases in LVEF (Mackey et al 2008):

Relationship of LVEF to Lower Limit of Normal (LLN)	Trastuzumab dose modification based on asymptomatic LVEF decrease from baseline		
	≤ 10 percentage points	**10-15 percentage points**	**≥ 15 percentage points**
Within facility's normal limits	Continue	Continue	**Hold** and repeat MUGA/ECHO after 4 weeks
1-5% below LLN	Continue [1]	**Hold** and repeat MUGA/ECHO after 4 weeks [1, 2]	**Hold** and repeat MUGA/ECHO after 4 weeks [2, 3]
≥ 6% below LLN	Continue and repeat MUGA/ECHO after 4 weeks [3]	**Hold** and repeat MUGA/ECHO after 4 weeks [2, 3]	**Hold** and repeat MUGA/ECHO after 4 weeks [2.3]

[1] Consider cardiac assessment and starting ACEI therapy.
[2] After 2 holds, consider permanent trastuzumab discontinuation.
[3] Start ACEI therapy and refer to cardiologist.

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • Once symptoms have resolved, if IR was not severe, consider resuming the infusion at a slower rate.	• Restart and re-challenge with pre-medications (e.g. H1-receptor antagonist and corticosteroid).
3 or 4	• Stop treatment. • Aggressively manage symptoms.	• Discontinue permanently (do not re-challenge).

Dosage with other toxicity:

Toxicity	Action
Pulmonary Toxicity	Discontinue permanently and manage symptoms aggressively with beta-agonists, antihistamines and/or corticosteroids. Discontinue permanently and do not re-challenge.

Dosage with Hepatic Impairment:

No adjustment required.

Dosage with Renal Impairment:

No adjustment required. The disposition of trastuzumab is not altered based on serum creatinine.

Dosage in the elderly:

No adjustment required; the risk of cardiac dysfunction and myelosuppression may be increased in elderly patients. The reported trials did not determine differences in efficacy between patients ≥ 65 years versus younger patients.

Children:

Safety and effectiveness in children have not been established.

back to top

F - Administration Guidelines

NOTE: Different trastuzumab products are **non-interchangeable.** There have been fatal reports where the incorrect trastuzumab product was administered to patients with breast cancer in the clinical trials setting.

- DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.
- Mix in 250 mL bag NS. Do not use D5W as it causes protein aggregation. Do not shake.
- Administer loading dose over 90 minutes. Observe during the infusion and for at least 90 minutes after the infusion.
- If no previous IR, subsequent infusions may be administered over 30 minutes. Observe patients during the infusions and for at least 30 minutes after the infusions.
- Should not be mixed or diluted with other drugs.
- Compatible with polyvinylchloride, polyethylene or polypropylene bags.
- Diluent supplied - Bacteriostatic Water for Injection (BWFI) - contains benzyl alcohol 1.1%; if patient is hypersensitive to benzyl alcohol, may reconstitute with Sterile Water for Injection, but must be used immediately and discard unused portion.
- Solution reconstituted with the supplied BWFI is stable up to 28 days refrigerated.
- Do not freeze the reconstituted solution.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Missed Dose

- If a dose is missed by 1 week or less, the product monograph recommends the usual maintenance dose (2 mg/kg if on a weekly schedule or 6 mg/kg if on an every-3-week schedule) should be administered as soon as possible (do not wait until the next planned cycle) and subsequent maintenance doses should be administered 7 or 21 days later (based on patient's maintenance dose/schedule)
- If a dose is missed by >1 week*, the product monograph recommends a re-loading dose (4 mg/kg if patient receives trastuzumab weekly; 8 mg/kg if on an every-3-week schedule) should be administered (over 90 minutes) as soon as possible, followed by the usual maintenance dose administered 7 or 21 days later (based on patient's maintenance dose/schedule).

  *For every 3-week dosing, consider repeating the loading dose for treatment delays ≥ 3 weeks (i.e.≥ 6 weeks from last dose). [Breast Disease Site Group consensus].

back to top

G - Special Precautions

Contraindications:

- Patients with known hypersensitivity to trastuzumab, Chinese Hamster Ovary (CHO) cell proteins, or any components of this product.

Other Warnings/Precautions:

- Trastuzumab should only be used in patients whose tumours overexpress HER2. Refer to product monograph for details on testing.
- The risk of cardiotoxicity must be weighed against the potential benefits of treatment, especially in older patients and patients who have had prior cardiotoxic therapy. Use extreme caution in patients with pre-existing cardiac dysfunction (including LVEF < 55% in early breast cancer). Note: in the adjuvant trials, patients with cardiac risk factors were excluded from the trials.
- Exercise caution in patients with pre-existing pulmonary disease, patients with extensive pulmonary tumour involvement or patients with previous chemo or radiation therapies known to be associated with pulmonary toxicities, as they may experience more severe lung toxicities.
- Patients with dyspnea at rest due to advanced malignancy complications and comorbidities should not treated with trastuzumab, as they may be at increased risk of a fatal infusion reaction or pulmonary events.
- Consider appropriate management of patients with uncontrolled hypertension or history of hypertension before starting trastuzumab.
- Trastuzumab and anthracyclines should not be given concurrently. Use with caution before or after anthracyclines (for up to 28 weeks after trastuzumab discontinuation due to long half-life).
- Life-threatening infusion-related reactions associated with the administration of trastuzumab may occur.
- Benzyl alcohol (a preservative in BWFI) has been associated with toxicity in neonates and children up to 3 years old.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Fetotoxicity: Yes
- Embryotoxicity: Yes
  Trastuzumab is not recommended for use in pregnancy. Impairment of fetal renal growth and/or function impairment resulting in oligohydramnios (including neonatal fatal cases) have been reported. Adequate contraception should be used by both sexes during treatment, and for at least **7 months** after the last dose. Monitor for oligohydramnios in patients who become pregnant during trastuzumab therapy. Perform appropriate fetal testing if oligohydramnios occurs.
- Excretion into breast milk: Yes
  (observed in animal studies)
  Breastfeeding is not recommended.
- Fertility effects: Unknown
  No data in humans; animal studies showed no evidence of impaired fertility.

back to top

H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Paclitaxel	↑ Trastuzumab level	↓ Trastuzumab clearance	Caution
Anthracyclines and other cardiotoxic drugs	↑ cardiotoxicity	Additive effects	Avoid concomitant use; exercise extreme caution with anthracycline-based therapy for up to 28 weeks after stopping trastuzumab

back to top

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Infusion-associated symptoms	During the infusion and observe for at least 90 minutes afterwards (for loading dose), and at least 30 minutes afterwards (maintenance dose)
Cardiac assessment, including evaluation of left ventricular function (Echocardiogram or MUGA scan);	Baseline, q3 months during treatment, then q6 months after trastuzumab discontinuation x2 years (and annually up to 5 years after last trastuzumab dose in adjuvant breast cancer patients who received anthracyclines), or longer if continued LVEF decrease, also as clinically indicated (more frequent monitoring in asymptomatic LVEF reductions)
Clinical exam for symptoms of cardiac failure, pulmonary toxicity and diarrhea	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Liver function tests	As clinically indicated
CBC	As clinically indicated

back to top

J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Trastuzumab (Biosimilar) - Second Line - Metastatic Breast Cancer
- Trastuzumab (Biosimilar) - Advanced Gastric, Gastroesophageal, or Esophageal Cancer
- Trastuzumab (Biosimilar) - Adjuvant Treatment for Breast Cancer
- Pertuzumab with Trastuzumab (Biosimilar) - Unresectable Locally Recurrent or Metastatic Breast Cancer
- Trastuzumab (Biosimilar) with Tucatinib and Capecitabine - Metastatic Breast Cancer
- Trastuzumab (Biosimilar) - Advanced or Recurrent Endometrial Cancer
- Trastuzumab (Biosimilar) in combination with Chemotherapy - Metastatic Breast Cancer
- Pembrolizumab and Trastuzumab (Biosimilar) - First-line Treatment of Advanced HER2-Positive Gastric or Esophagogastric Junction Adenocarcinoma

back to top

K - References

Leyland-Jones B, Gelmon K, Ayoub JP, et al. Pharmacokinetics, safety, and efficacy of trastuzumab administered every three weeks in combination with paclitaxel. J Clin Oncol. 2003 Nov 1; 21(21):3965-71.

Mackey JR, Clemons M, Cote, MA, et al. Cardiac management during adjuvant trastuzumab therapy: recommendations of the Canadian trastuzumab working group. Current Oncology 2008; 15: 24-35.

McEvoy GK, editor. AHFS Drug Information 2011. Bethesda: American Society of Health-System Pharmacists, p. 1252-8.

Petalozzi B, Brignoli S. (Letter to the editor) Trastuzumab in CSF. J Clin Oncol 2000;18(11):2350-1.

Prescribing information: Herceptin (trastuzumab). San Francisco, CA: Genetech Inc; November 2018.

Product monograph: Adriamycin® (doxorubicin). Pfizer Canada Inc., July 9, 2014.

Product monograph: Herceptin® (trastuzumab). Hoffmann-La Roche Ltd., November 2018.

December 2024 Added new NDFP form

back to top

L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an “as-is” basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information’s quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary’s content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person’s use of the information in the Formulary.

back to top